To

my wife

ANNETTE

NATURE OF RHEUMATIC HEART DISEASE

With Special Reference to Myocardial Disease and Heart Failure

BY

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With 162 Photomicrographic Illustrations in Color



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With Special Reference to Myocardial Disease and Heart Failure*

GEORGE E MURPHY M.D

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* From the Department of Pathology of the New York Hospital-Cornell Medical Center
The findings in ventricular myocardium and in atrial appendage of the heart that are here illustrated were in large part presented on April 4th 1959 before the 15th General Assembly of the Japan Medical Congress in Tokyo

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IN APPRECIATION

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Over the past 300 years observations have shown that many tissues especially vascular structures throughout the body are often injured in attacks of rheumatic fever (122 a 124 176-a) The most serious damage occurs in the heart to its muscular substance and to its valves Information laboriously collected and correlated in the past 80 years has shown that infections with group A hemolytic streptococci play a causative and key role in the pathogenesis of this disease (32 52 101 116 a 124-a 128 145 a 146 164 175 a) However many of the most important aspects of the pathogenesis are still poorly understood How interaction of the streptococci with the host is related to the development of rheumatic disease of the heart and other tissues in only a small proportion of the very many human beings who are repeatedly infected with these microorganisms has not been established Knowledge that has been gained by experiment concerning this question will be reported in this monograph

It appears probable that hereditary factors are important to the development and outcome of attacks of rheumatic fever (63 a 170-a 203 a) It is also probable that the relationship to one another of a complicated series of pathogenetic events is important to the natural history of rheumatic disease For example in the case of a given patient events that occur well in advance of an attack of rheumatic fever manifested by obvious polyarthritis and/or chorea and by *insidious* heart disease at 5 years of age are important to the development and outcome of this attack The outcome of this attack in turn may be of great importance to reaction of the heart and other tissues to subsequent events that may lead eventually to the development of intractable heart failure 15 or 50 years after the rheumatic attack at 5 years of age In such cases there may be strong clinical evidence of one or more attacks of active rheumatic disease in the long interval between the attack at 5 years of age and the onset of heart failure many years later But in other such cases there may be detected in this interval either little or no evidence of active rheumatic disease other than the important change in some cases from year to year or decade to decade of auscultatory signs indicating that progression of rheumatic heart disease has occurred We now know however that active rheumatic heart disease is often present, sometimes in protracted form without fever and beneath the clinical horizon and in reference to this form of the disease the term rheumatic fever appears to be inappropriate Indeed a large proportion of adults with severe chronic rheumatic heart disease do not recall their having experienced any attack of rheumatic fever or chorea We also know that infections with group A streptococci may sometimes be so mild as to go unrecognized by patient or physician Among the principal questions to be answered concerning rheumatic disease is the following Why in some patients does active rheumatic heart disease continue for prolonged period causing progressive cardiac damage sometimes without evidence of the activity from clinical or laboratory investigation and sometimes without serological evidence of recent streptococcal infection?

In view of the complexity of the pathogenesis of rheumatic heart disease the production with regularity of the disease in animals would be of great value Very important in this endeavor and essential to understanding of the nature of rheumatic heart disease is understanding of the origin and development of morphologic changes in the heart and their relation to altered cardiac function in this disease As Opie (133 a) has written The functional aspect of disease determines its outward manifestation and is that from which we suffer These outward manifestations and their underlying physiological basis are inseparable from structure which is not more static than function He further wrote Pathogenesis is a moving picture of disease to be considered from every standpoint and with special emphasis on causation Nevertheless some aspects of disease tend to be neglected in so far as morphologic phenomena are ignored That deformity of cardiac valves following protracted or repeated attacks of rheumatic valvular disease places an important and sometimes disabling burden on the heart is well recognized and has been emphasized for many years (39) However it appears to the author that there is widespread neglect and lack of

understanding of the morphologic changes in the myocardium and of their relation to altered function and failure of the heart in rheumatic heart disease Structural and functional integrity of heart muscle cells is clearly of primary importance to normal function of the heart The long held and now very widely accepted concept that rheumatic lesions of the myocardium, including the so called Aschoff bodies are nonmyogenic lesions of connective tissue fails to explain the altered function and failure of the myocardium in this disease Furthermore strong evidence demonstrates that this concept is incorrect This evidence, acquired from experiment and detailed histopathologic study and observable under a wide variety of conditions, has been assembled and is now submitted to demonstrate that rheumatic lesions in the myocardium including the so-called Aschoff bodies originate and develop from rheumatic injury to heart muscle cells themselves Moreover these findings when viewed in relation to clinical observations provide evidence of the important causative relation of rheumatic disease of the myocardium to altered function and failure of the heart in rheumatic heart disease in children and adults

That attacks of rheumatic fever can damage the heart was recognized by Pitcairn (141) and by Jenner (84) in 1788–89 In 1816 Laennec invented the stethoscope Aided greatly by use of this instrument Bouillaud who first used the terms endocardium and endocarditis (21) detected signs of heart disease in a large proportion of patients with acute articular rheumatism and he attributed this heart disease to rheumatic involvement of cardiac valves and pericardium In 1840 he stated the following

In the great majority of cases of diffuse acute articular rheumatism with fever there exists in variable degree a rheumatism of the sero-fibrous tissues of the heart The coincidence is the rule and the non-coincidence the exception (22)

Substantial evidence that the myocardium can be involved in rheumatic disease was not acquired until the end of the 19th century Previous to that time Itard (79) in 1824 believing that skeletal muscle is often involved in rheumatism speculated that the heart because of its essential muscular structure surely is one of the viscera which should be most likely the site of rheumatic inflammation and he conjectured that rheumatism may involve primarily the muscle of the heart without affecting such external structures as the joints In 1876 Besnier (16) without histologic evidence surmised concerning the then little considered possibility of rheumatic injury to cardiac muscle as follows

This injury occurs frequently if not absolutely regularly and can be observed in advanced degree without considerable damage to the endocardium or pericardium

Knowledge concerning rheumatic lesions of heart muscle cells and their important relation to cardiac failure in rheumatic heart disease has been acquired slowly Primarily because of the widespread lack of recognition of the myogenic nature of rheumatic lesions of the myocardium and the strong influence of the concept of collagen disease or disease of connective tissue the importance of alteration of heart muscle cells to altered function and failure of the heart in rheumatic heart disease has been widely neglected After discussing the pathologic physiology of cardiac valves and pericardium in rheumatic heart disease Coombs (39) wrote in 1924 as follows As we pass to the more important morbid physiology of the myocardium it is well that we should be reminded that lesions of the serous layers are of importance only in so far as they tend toward the final defeat of the cardiac muscle In essence the heart is a muscle its functions and properties are muscular and depend in the last resort on the condition of the cells of the myocardium

I Purpose of This Communication

In this communication evidence is presented to demonstrate the origin of Aschoff bodies and other lesions from muscle cells in rheumatic heart disease This evidence stems from the experimental induction of myocardial lesions closely resembling those of human rheumatic heart disease in a small proportion of many rabbits of random stock that were repeatedly infected focally with group A streptcocci (123 127 128) Results of these experiments provide evidence that Aschoff bodies and other myocardial lesions in human rheumatic heart disease result from repeated focal infections with group A streptococci even though these lesions develop in only a small proportion of the many in the random population so infected Further evidence of the close resemblance of the naturally-occurring and experimentally induced myocardial lesions is here submitted

From detailed microscopic study it has been found that the experimentally induced lesions are derived from injury to heart mu cle cells This experimental investigation has led to ex tensive direct evidence of the origin of A choff bodies and other myocardial lesions from heart muscle cells in human rheumatic heart disease These latter findings some of which have been previously reported (123, 126) have resulted from intensive and detailed microscopic study in the past ten years of the heart of over 100 patients who died with active rheumatic heart disease and of the left atrial appendage removed from over 150 other patients at the time of mitral commissurotomy The evidence so ob tained and here illustrated is in striking con trast with the very widely accepted concept that the e myocardial lesions are non myogenic le sions of connective tissue Furthermore study of myocardial arteries atrial appendages and car diac valves has led to the finding of the hitherto unrecognized origin of certain rheumatic lesions from *smooth* muscle cells and some of the e latter lesions can as here illustrated re emble to varying degrees Aschoff bodies that are derived from heart mu cle cells

Experimental and histopathologic findings here presented are viewed and discussed in re- lation to clinical observations to show the im portant causative relation of rheumatic disease of heart muscle cells to altered function and failure of the heart in acute and chronic rheu matic heart disease in children and adults

The histopathologic evidence illustrated at the end of this communication is in the form of color photolithographs that were made without hand retouching or dot etching from the original photographic transparencies The material il lustrated is from the following sources

1) Heart or skeletal muscle examined at the time of autopsy of 36 patients comprising 23 females and 13 males with rheumatic heart disease who died at ages ranging from 17 months to 70 years (24 patients at New York Hospital 6 at Rockefeller Institute Hospital 2 at Babies Hospital 1 at Mount Sinai Hospital 1 at Belle vue Hospital and 1 at New York Nursery and Child s Hospital all in New York City and 1 at Johns Hopkins Hospital), among these 36 pa tients lesions specific for active rheumatic heart disease were found in 31

2) Left atrial appendage of 10 patients com prising 9 females and 1 male whose ages ranged from 29 to 55 years when the appendage was surgically removed at the time of mitral com missurotomy at the New York Hospital in 7 of these patients there were found lesions specific for active rheumatic heart disease

3) Heart or skeletal muscle of 16 rabbits (15 died 1 was sacrificed while very ill after focal group A streptococcal infections), comprising 5 rabbits of *random* stock and 11 rabbits of stock *specially bred* in long term experiments that are continuing In brief explanation of the spe cially bred stock it should here be emphasized that among the very many rabbits of random stock that have in the past several years been repeatedly infected focally with group A strep- tococci only a few have developed lesions like those of rheumatic heart disease and it is note worthy that rheumatic fever (and rheumatic heart di ea e) develop in only a few among the random human population who experience re peated infections with group A streptococci The occurrence however of rheumatic fever (and rheumatic heart disease) in high incidence in certain human families motivates our striving to develop by special breeding families of rab bits analogous to these human families with respect to development of lesions of rheumatic type Several years ago an initial group of breeders were selected from 91 rabbits of 17 litters of known parentage from random stock of the Rockefeller Institute by testing their reactivity to repeated focal infections produced in sequence by group A streptococci of the fol lowing erological types Type 19 Type 1 Type London and Type 3 Approximately one month elapsed between the first and second and be tween the econd and third infections and ap proximately two months between the third and fourth infections In a rabbit of random stock this system of infections had previously resulted in a fatal illness associated with marked ir regularity of cardiac rhythm 10 days after the last infection In the heart of this rabbit were found microscopically a variety of lesions of rheumatic type involving myocardium cardiac valve and myocardial arteries The capacity of rabbits to develop cardiac lesions after focal streptococcal infections is obviously difficult to ascertain during life in the animals and micro copic study is the most reliable means of verification Nevertheless after two or more of the infections outlined above signs and symp- toms have occurred which have supplied us

with the following criteria for use in selection of 'positive reactors for further breeding 1) Cutaneous hyper reactivity to reinfection, 2) evidence of general illness i e, weight loss sustained anorexia, elevated erythrocyte sedimentation rate 3) abnormal cardiac rhythm, development of heart sounds of poor quality including slurring and muffling and finally of greatest value development of cardiac murmurs Auscultation with regularity of rabbit hearts in the last several years has indicated that the development of systolic murmurs both transient and permanent is very valuable to the detection of heart disease in selection of positive animals for further breeding and stethograms from the animals made with an electrocardiograph stethograph unit (Cambridge Instrument Co) give visual proof of these murmurs When rabbits die after two or more infections and their hearts show active lesions or scars *their siblings that have most positively reacted* to streptococcal infections are set aside for further breeding The occurrence of scarring in valves myocardium and myocardial arteries in addition to occurrence of active lesions in these sites is of importance to us from several points of view including correlation of cardiac lesions with abnormal cardiac signs in life and choice of positive siblings for further breeding

The photolithographs in Plates I and II illustrate the close resemblance between the so called Aschoff bodies in man and myocardial lesions experimentally induced by us in rabbits by repeated focal infections with group A streptococci Further evidence of the close similarity of human rheumatic and the experimentally *induced myocardial lesions is found* in Plates VI VIII and XVII The figures in Plates II through IX and in Plate XVIII illustrate the origin of Aschoff bodies from heart muscle cells The figures in Plate IX pointedly illustrate the occurrence of Aschoff bodies in the absence of demonstrable change in connective tissue and this is also illustrated in many figures of other plates In Plate X the origin of subendocardial Aschoff bodies from heart muscle cells in atrial appendages and the striking resemblance of *these lesions to a ventricular* subendocardial Aschoff body (Fig 87) is demonstrated The figures in Plates XI XII XIV and XV taken together illustrate the origin of rheumatic lesions from smooth muscle cells in cardiac atria valves and myocardial arteries, and it can be seen that some lesions of smooth muscle cells in these sites can resemble to varying degree Aschoff bodies that are derived from (striated) heart muscle cells The occurrence of heart muscle fibers in cardiac valves is illustrated in the figures of Plate XIII In Plates XVI and XVII can be seen a variety of rheumatic lesions that are derived from *heart muscle cells*

Pertinent clinical information and histopathological descriptions accompany the photolithographs Figs 9 49, 51 56 58 62 65 92 95 109 121 122 151 and 154 are from rabbits of stock specially bred as outlined earlier in this section

Our experimental and direct histologic findings concerning rheumatic lesions of muscle cells in the heart are discussed in detail in sections V through IX of the text of this monograph In the interest of achieving historical perspective these *sections are preceded by detailed historical sec*tions on cardiac dilatation in active rheumatic heart disease the earlier observations on the histopathology of the myocardium in rheumatic heart disease and the culmination in recent years of the concept that the characteristic rheumatic myocardial lesions are non myogenic alterations of connective tissue In sections X and XI evidence is given of the important causative relation of rheumatic disease of heart muscle cells to altered function and failure of the heart Finally in sections XII and XIII there are respectively discussions of the relation of rheumatic lesions of blood vessels in the heart to myocardial damage and the relation of valvular deformity to myocardial function and failure

II CARDIAC DILATATION IN ACTIVE RHEUMATIC HEART DISEASE

In fatal cases of active rheumatic heart disease the ventricular chambers particularly the left are generally dilated sometimes markedly Such dilatation may be seen when neither valvular deformity nor *pericardial adhesions are* present and is associated with dilatation of the atrio-ventricular valve rings (39 51, 104 105 199) On this point Coombs (39) in 1924 wrote as follows If the heart of a child dying during an active phase of cardiac rheumatism be looked at the fact that *will* at once strike the observer is the enlargement of the ventricles Before the heart is opened this is chiefly apparent as a widening of the heart due to increase of the transverse diameter of the ven

tricle which gives the organ an unduly globular appearance When the ventricles are open it is found that their cavities are widened in the same way As a rule this is especially noticeable in the left ventricle The normal ventricle when examined post mortem is found to have scarcely any cavity but in these cases there is a quite considerable space to be seen

In 1878 (sixteen years before Bret s and twenty six years before Aschoff s and Tawara s description of the lesions now known as Aschoff bodies) West (199) reported the case of a young woman who showed rapid cardiac enlargement and died five days after the onset of migratory polyarthritis At autopsy normal heart valves no evidence of pericarditis and no pericardial effusion were found but the left ventricle was considerably dilated The myocardium showed several pale patches and West further observed Microscopic examination showed that in these white patches the muscular tissue had undergone acute granular (fatty) degeneration its fibers being converted into granular cylinders There was no interstitial growth After viewing in the light of this case two other patients with acute rheumatic fever who showed for many days signs of acute cardiac dilatation with feeble heart sounds and without evidence of pericarditis West concluded It is possible that more extended and careful observation may show that such dilatation is not by any means so uncommon as is usually thought It is capable we know of producing murmurs which usually disappear with convalescence and if as seems possible this dilatation has for its cause organic change in the muscular fiber a reasonable explanation is provided of the true pathogeny of many of the so called anemic or blood murmurs of rheumatic fever and a caution is given as to the need of the most careful treatment of such cases Fisher (51) in 1896 concluded from clinical pathological analysis that mitral insufficiency that develops during attacks of rheumatic fever is due to dilatation of the left ventricle rather than to valvular inflammation or deformity

Lees and Poynton (104 105) submitted extensive evidence of acute cardiac dilatation in attacks of rheumatic fever in children and young adults After outlining by careful percussion the area of cardiac dullness they made serial tracings of this area (without reference to previous tracings in each case) and demonstrated during rheumatic attacks an increase in the area of cardiac dullness that was followed by diminution in the size of this area as improvement occurred They also demonstrated increase in the area of cardiac dullness during recurrent attacks Investigation at autopsy by Herringham (104) of patients from whom tracings of cardiac outline had been made were cited by Lees to show that their tracings of the cardiac outline obtained by careful percussion indicated with considerable accuracy the position of the limits of the heart both to the left and to the right As control material they used tracings of the area of cardiac dullness in 80 children who were free of rheumatic heart disease From analysis of the post mortem records of the Great Ormond Street and St Mary s hospitals in London of 150 cases of fatal rheumatic heart disease in children under twelve years of age they found that in 92 cases (61%) special mention had been made of cardiac dilatation in the autopsy records and in 58 cases (38%) the dilatation had been recorded as marked On the other hand excess of pericardial fluid was uncommon in only 12 of the 150 cases was more than two ounces noted Coombs (36) in 1907 stated that in the great majority of children with rheumatic fever studied by him the signs of cardiac disease were referable to ventricular dilatation and its corollary mitral incompetence Of the common dilatation of atrio-ventricular valve rings he later wrote (39) Slung in the midst of cardiac muscle as these rings are it is not wonderful that they should participate in the general stretching which the musculature of the heart undergoes as we have seen in cardiac rheumatism

III EARLY OBSERVATIONS ON THE HISTOPATHOLOGY OF THE MYOCARDIUM IN RHEUMATIC HEART DISEASE SPECIAL REFERENCE TO THE SO CALLED ASCHOFF BODIES FIRST CLEARLY DESCRIBED BY BRET

In a fatal case of rheumatic fever Goodhart (63) in 1879 observed on microscopic study of the heart with widely dilated left ventricle a considerable quantity of interstitial cell growth around the vessels and between the muscular fasciculi In 1887 Cadet de Gassicourt (27) wrote that in the myocardium attacked by inflammation in rheumatic fever the irritative process which develops in the depth of the muscular substance is rendered evident by the de

formation of the muscular nuclei and by the proliferation of cellular interstitial growth He considered rheumatic lesions of the myocardium to represent interstitial myocarditis Krehl (94) in 1889 reported finding in the myocardium interstitial changes that he interpreted to be progressive and various degenerative changes associated with proliferated intimal and medial elements with narrowing of the lumen of medium sized and small myocardial arteries He considered these changes to be more important to heart failure than valvular deformity He further suggested that precordial pain in rheumatic fever is directly related to vascular lesions in coronary arteries and analogous to the pain of angina pectoris associated with coronary arteriosclerosis In 1894 Romberg (153) reported on the occurrence in the heart in two fatal cases of rheumatic heart disease of numerous small indurations composed of connective *tissue which were rich in nuclei and in newly* formed blood vessels and he further observed in many sites large cells and in one place poorly stained greatly elongated and distended nuclei

In the same year Bret (24) published a detailed microscopic description of the myocardium in a seventeen year old girl who died during an attack of acute rheumatic fever After describing embryonic proliferation in the form of numerous and disseminated foci near arterioles in the subepicardial area of the myocardium he further described the following 'Independent of these embryonic perivascular proliferations there *exist deep in the cardiac muscle at a consider* able distance from the inflamed pericardium other foci which appear absolutely independent of all connection with blood vessels or connective tissue They are for the most part rounded masses or elongated trails parallel to the direction of the muscle bundles, and in the interstices of the latter They appear to be of uniform constitution which is approximately the following the central part of these inflammatory foci is formed of opaque caseous blocks that stain very strongly they appear to result in our opinion from degeneration of cardiac muscle fibers At their periphery are arranged a multitude of embryonic elements In certain much smaller foci where the coalescence of these latter is less one sees very distinctly in the fibers that are destined to degenerate that the nucleus is enormously enlarged and becomes opaque

The above description by Bret appears to be the first clear description of the lesions that are now known as Aschoff bodies Bret also described extensive changes in the myofibers of the papillary muscles of the left ventricle, and of this change he wrote as follows At some distance from the connective tissue and vascular regions the alterations of the fibers are considerable They show for the most part as described by Lepine and Mollard, a considerable exaggeration in the longitudinal striations, the fibrillar elements, considerably spread apart one from the other present the aspect of bristles spread apart in a metallic brush Some fibers in great numbers, appear empty, the clear spaces occupying one-third or one half of the transverse area of the cardiac cell Finally at a more advanced stage of this same lesion, the neighboring fibers lose *their individuality melting into a granular mass* devoid of nucleus and with granules representing with certainty the persistent primitive cylinders

Renaut (147) in 1899, with respect to changes in the nuclei of heart muscle fibers in rheumatic fever wrote as follows The nuclei can increase in number, and in this manner reinforce the cellular defense by multiplying in the elements involved in the struggle In the same year Poynton (142) described in the myocardium foci of cellular exudation spreading from the blood vessels and cellular exudation between the muscle fibers in addition to numerous foci of fatty change in heart muscle cells in cases of rheumatic fever In 1902 Janot (82) reported that in three cases of acute rheumatic myocarditis studied by him the cardiac muscle fibers were affected almost exclusively In one case, that of a seven year old girl he reported change in the myocardium as follows The connective tissue appears not at all affected in our sections except at one point which is an old lesion The intense and recent lesion is exclusively parenchymatous In his second case he reported that the myocardial lesions involved the muscle cells only, and in his third case he reported vacuolar alterations of the muscle cells with a weak connective tissue reaction

In 1904 Aschoff (3) reported on Tawara's study with him of the hearts of five patients with articular rheumatism and he stated that they had confirmed the findings of the Leipzig

school (Krehl and Romberg) regarding the general occurrence of interstitial change in the myocardium associated with valvular insufficiency As a feature of this change they described in the hearts of two of these patients peculiar nodules which appear to be specific for the rheumatic myocarditis They observed these nodules in the neighborhood of small or medium sized blood vessels and they further wrote The aforementioned nodules are unusually small mostly submiliary, and originate by the conglomeration of large elements with one or more abnormally large indented or polymorphic nuclei The arrangement of the cells frequently occurs in the form of a fan or a rosette The periphery is formed by the large nuclei the center by the paler or colorless appearing necrotic mass of confluent cell protoplasm This description is strikingly like that reported ten years earlier by Bret Aschoff believed that the giant cell like large nucleated elements in these nodules are derived from adventitial cells of blood vessels He and Tawara were unable to explain the symptoms of heart failure in rheumatic patients on the basis of the interstitial myocarditis with or without nodule formation and because they could find no histologic pattern for the failure of the muscle mass it was necessary to consider that not the muscle mass as such but only a certain part was injured namely the so-called atrioventricular bundle which gives automaticity according to the myogenic theory But in none of three cases of rheumatic fever with specific myocardial nodules could Tawara find after detailed study alteration of the atrioventricular bundle to explain the heart failure In discussion of Aschoff s report Zur Myokarditisfrage Babes stated that in my experience the changes in muscle cells and nuclei in myocarditis are not so insignificant as it appears Herr Aschoff assumes Furthermore he stated that in tuberculous and syphilitic myocardial lesions giant cells that he had observed were derived from muscle cells and he referred to a case of chronic endocarditis in which he had demonstrated a peculiar form of segmentation of heart muscle fibers Also in the discussion Busse reported that the giant cells in large numbers that he had found in hearts with syphilitic inflammation undoubtedly originated from muscle fibers and Schmorl on the same occasion reported that he had confirmed Fiedler s report on the origin of giant cells from muscle fibers in cases of idiopathic myocarditis

A year later Geipel (57) in 1905 reported results of his studies begun in 1903 on the myocardial lesions in rheumatic fever In fourteen cases he found nodules like those reported by Bret (24) in 1894 and by Aschoff observed that these lesions occurred at some distance as well as close to blood vessels and considered that they were specific for rheumatic fever In agreement with Aschoff he believed that the large cells arose from wandering vascular adventitial cells but in contrast with the view of Aschoff he believed that these cells were called out in reaction to a primary degenerative change in connective tissue in particular swelling followed by necrosis of collagen He also conceived that in these lesions the intercellular connective tissue substance becomes fibrillar He ascribed damage to heart muscle cells to atrophy caused by the pressure of adjacent rheumatic nodules In a fifteen year old boy who died with acute rheumatic heart disease Geipel (58) found various degenerative changes in many skeletal muscles and he considered that these lesions of skeletal muscle were not specific for rheumatic fever In the following year Aschoff and Tawara (6) again denied the origin of the large cells from heart muscle cells and suggested that they were possibly lymphocytoid cells They believed that a rheumatic virus calls out a proliferative reaction of these cells and that necrosis of the centrally located proliferated cells is a secondary occurrence Saigo (158) in 1908 briefly mentioned that some of the giant cells in Aschoff bodies in one rheumatic heart he had studied might be of myogenic origin whereas the other large cells in these lesions he considered to be epithelioid cells In the same year Coombs (37) suggested that the characteristic rheumatic myocardial nodules represent a peculiarly definite type of connective tissue reaction at the actual points of infection by microorganisms and in 1910 (38) he drew the analogy of the Aschoff body in the myocardium standing in relation to the subcutaneous nodule as a miliary tubercle stands in relation to a large tuberculous mass Thorel (182) in the same year interpreted Aschoff bodies as developing from a peculiar primary focal degeneration of muscle or connective tissue that is associated with abortive regenerative changes in the muscle fibers and proliferation of neighboring con

nective ti ue cells , and he believed the e le ions are reactions to diplostreptococci De Vecchi (188) in 1912 considered that Aschoff bodies are reactions to focal myocardial necrosis produced by a rheumatic virus Frank (53) in the same year stated that the primary and essential process repre ented by rheumatic subcutaneous nodules is exudation followed by an inflammatory reaction associated with proliferation of connective ti sue elements and in turn by organization of exudate A core of homogeneous material taining intensely red with eosin he believed to be fibrin

Tilp (183) concluded that nodules found in galea aponeurotica were histologically like tho e in subcutaneous tissue and like the nodules de cribed by Aschoff in the myocardium However Huzella (77) in 1914 reported the occurrence of keletal mu cle lesions very similar to Aschoff bodies in two cases of rheumatic fever He thought he could trace the origin of giant cells in these le ions from mu cle cells and by analogy he suggested that some giant cells in Aschoff bodies may originate from heart muscle cells But in discu sion of Huzella s report Aschoff and Frankel strongly insisted that all Aschoff bodies are lesions of connective ti sue elements and do not compri e myogenic elements In 1919 Jacki (80) concluded from study of subcutaneous nodules that the e lesions represent e sentially a proliferative reaction which can be accompanied by exudation of fibrin and she considered that these le ions and Aschoff bodies are genetically similar with small differences being accounted for on the basis of different ground sub tances in various ti sues In the following year Mallory (112) interpreted the characteristic rheumatic myocardial le ion as repre enting collagen attacked and di solved by the action of endothelial leukocytes which sometimes form multinucleated cells However in the same year Whitman and Eastlake (202) reported that they could trace in an area of myocardium in one rheumatic heart the origin of some cells in Aschoff bodies from myofibers and in the same year Huzella (78) in follow up to his report given in 1914 stated that the characteri tic constituents of rheumatic nodules are myogenic and I have found this structure nowhere out ide the heart and skeletal mu culature Fahr (49) in 1921 differentiated the myocardial nodules on the one hand from subcutaneous and synovial le ions on the other on the ba is of predominant cellular proliferation in the first case and prominent fibrinous exudation in the latter two lesions Swift (174) and Coombs (39) in 1924 in agreement with Jacki on the essential similarity of the ubcutaneous nodules and the myocardial Aschoff bodies concluded, as Mallory had in the case of the Aschoff bodies that the characteristic large cells in both le ions develop from vascular endothelium and Coombs suggested that proliferating va cular endocardial cells can imitate the large cells of the Aschoff body A year later MacCallum (110) wrote concerning the remarkable large cells in Aschoff bodies , that everyone agrees they are peculiar to rheumatism and that the large cells are not derivatives of the mu cle cells of the myocardium In contrast Letulle Bezançon and Weil (106) in 1926 submitted histologic evidence in a case of fatal rheumatic fever that was very suggestive of the formation of giant cells from cardiac mu cle fiber which they considered to be the result of fragmentation of myofibers and amitotic division of their nuclei Symmers (177) in 1928 though he ubmitted no evidence stated that in Aschoff bodies the heart muscle fibers themselves appear to suffer damage followed by an attempt to regenerate with formation of multinucleated giant cells He further stated that he could see no histological relation hip between subcutaneous nodules and Aschoff bodies A year later Graff (64) distinguished between two forms of reaction in rheumatic fever 1) the Aschoff bodies comprising predominantly proliferated mobile cells that he conceived could become fused and 2) the extracardiac lesions such as those in tendon heath that he believed compri e changes of collagen fibers and other connective tissue elements with proliferation of cells

IV CULMINATION IN RECENT YEARS OF THE CONCEPT OF CONNECTIVE TISSUE ORIGIN OF THE SPECIFIC RHEUMATIC LESIONS IN THE MYOCARDIUM THAT ARE GENERALLY KNOWN AS ASCHOFF BODIES

In 1880 Neumann (131) described in inflammation of erou synovial and mucous membranes and of vascular intima and endocardium what he interpreted to be a certain structural alteration in connective tissue for which he introduced the term fibrinoid degeneration and he referred to the product of this change as fibrinoid sub tance because it resembled and tained like fibrin He interpreted verrucous

endocarditis as probably representing inflamed proliferated valvular tis ue which had undergone the de cribed fibrinoid metamorphosis but he found the differentiation from layered thrombotic mas.es of fibrous material to be very difficult In 1896 Neumann (132) reported extension of his ob ervations on fibrinoid degeneration in inflammation in synovia pleura pericardium endocardium peritoneum and in diphtheritic inflammation in the mucous membrane of the trachea In addition he described fibrinoid substance in the wall of tuberculous cavities He concluded that this substance represented a fibrin like transformation of collagen fibers At this time he al.o stated that he was convinced that verrucous endocarditis is the product of fibrinoid degeneration of connective ti sue

In the same year Marchand (116) concluded that fibrinoid degeneration of connective tissue belongs to the vague ideas of pathology which are only suitable for be fogging well investigated proces es and for this rea on must be discarded

The views of Talalajew summarized by him in 1929 (178) amplified the concept that rheumatic lesions develop from primary alteration of connective tissue He suggested that there are three phases in the life cycle of rheumatic lesions 1) primary exudative-degenerative change in connective tissue 2) a econdary proliferative process with development of syncytial masses and finally 3) a sclerotic or healing pha.e He wrote as follows The views of Frank Thorel and Geipel were brought together by Talalajew in a omewhat different formulation The exudative-degenerative changes in the intermediary substance of the connective ti sue (stage of disorganization) he presumed to be primary and the proliferative changes econdary Of his conception of this primary change Talalajew wrote

In cases of acute rheumati m with early fatal termination there are seen to develop first for the localization of the rheumatic granuloma typical foci of a myxomatous edema with typical ba ophilic diffuse discoloration and basophilia of the collagenous fibrous tissue develops And he further wrote The collagenous bundles swell and become homogeneous Al o there is swelling of the cellular elements an increase of their circumference and an ob ervable destruction of occa.ional cells This stage of the rheumatic proce s we have designated as the exudative degenerative that is characterized by myxomatous edema and degeneration of the intermediary substances Proliferation of cells is lacking In the extra cardial localizations there is added to the e changes a prominent deposit of fibrinous exudate In the case of the myocardial localization of the process the exudative-degenerative moment is usually weak and the process appears to begin with a primary cellular proliferation which is in accord with the views of Aschoff In the ca.e of what he referred to as fibrinoid substance in Aschoff bodies Talalajew left the question open as to whether it repre.ents fibrinous exudate or fibrinous tran.formation of the collagenous substance Talalajew further wrote If one takes into consideration principally the extra cardiac localizations of the rheumatic process which are usually considered to be pathogenetically the same as the alterations in the heart one must emphasize that the exudative degenerative stage is especially clear and unequivocal

From 1930–33 Klinge (91) and associates reported results of extensive studies on the pathology of rheumatic fever They concluded that their findings fully confirmed the view of Talalajew that the basic and characteristic rheumatic lesion in whatever tissue of the body it occurs is essentially a degenerative change in the connective tissue They wrote as follows In this primary lesion which exhibits a swelling of the ground substance of the connective ti.sue with subsequent degeneration we believe that one sees the e.sential change found in all rheumatic lesions From this primary lesion there develops —by proliferation of the mesenchyme cells—the cellular nodules the mo t distinctive form of which is the A.choff heart nodule Klinge stated that the earliest change is in the collagen fibers and he called this change Fruhinfiltrat (rheumatische Fruhinfiltrat des kollagenen Bindegewebes) and this change he conceived to be followed by a degeneration of the interfibrillary substance of the collagen fibers that then acquire the property of staining like fibrin (fibrinoid degeneration) The acute stage of Fruhinfiltrat and fibrinoid degeneration of the collagen fibers (akutes degenerative exsudatives Stadium) he conceived to be followed by a subacute chronic granulomatous stage (granulomato es Stadium des Zellknotchens) the stage of the fully developed A choff body in which there is proliferation of me enchymal connec

tive tissue cells in reaction to the collagen damage, and this is followed by scar formation ('Narbenstadium') Klinge illustrated in systematic drawings in color his concept concerning the sequence of changes in collagen fibers That muscle cells are not directly involved in myocardial nodules Klinge believed could not be questioned But he recognized that heart muscle cells are often damaged in rheumatic fever, and he attributed this damage in some instances in agreement with Geipel to pressure exerted by Aschoff bodies on contiguous muscle cells and in other instances to direct rheumatic injury to muscle cells

In 1901 Menzer (121) suggested that acute rheumatism develops in certain individuals who because of hereditary or acquired conditions react in a special way to infection with various microorganisms especially pathogenic streptococci in the mouth Schick (163) in 1907 suggested that the *Nachkrankheiten* of scarlet fever including migratory polyarthritis and heart disease are allergic reactions Friedberger and Cederberg (55) in 1913 reported that rabbits sensitized to foreign serum developed striking joint swelling 5 to 6 hours after intra articular injection of the same foreign serum and Weintraud (197) in the same year concluded that rheumatic fever is an anaphylactic reaction due to a secondary allergic condition caused by infection In cutaneous Arthus reactions in rabbits made hypersensitive to sheep serum Gerlach (59) in 1923 reported perivascular lesions and swelling of collagen fibers (the present author sees no fibrinoid material in the lesions in Gerlach's illustrations) Klinge (91) in 1929 produced arthritis by injecting horse serum into the knee joints of rabbits sensitized to horse serum He interpreted the reaction in the rabbit joints as representing essentially a degenerative process in the connective tissue ground substance in which 'fibrinoid necrosis was a prominent feature and he likened these changes to those in human rheumatic polyarthritis He also described in some of the sensitized rabbits perivascular lesions in the heart that he considered to be analogous to Aschoff bodies Vaubel (187) and Junghans (85) induced arteritis in the heart and other organs and valvular endocarditis in rabbit by repeated parenteral injections of foreign serum Vaubel interpreted some of these vascular changes as representing fibrinoid swelling of collagen and he considered that some of the lesions resembled those of periarteritis nodosa thrombo angiitis obliterans and especially rheumatic arteritis Klinge Vaubel and Junghans concluded that their animal experiments supported the concept that hypersensitivity is the basic pathogenetic mechanism in rheumatic fever and Klinge extended this pathogenetic hypothesis for rheumatic fever to several human diseases on the basis of the occurrence of lesions that he considered to represent fibrinoid degeneration of connective tissue Hence rheumatoid arthritis periarteritis nodosa thrombo angiitis obliterans dermatomyositis certain nephritides, and malignant nephrosclerosis were regarded by him as conditions with an allergic basis By the same token Rossle (154) and Jaeger (81) believed that fibrinoid degeneration of collagen is a characteristic and constant morphological feature of diseases of allergic or pathergic background and proposed that such diseases as rheumatic fever rheumatoid arthritis periarteritis nodosa, and thrombo angiitis obliterans should be designated as the rheumatic group of diseases

From 1930–33 Gross and Ehrlich (69 70) reported on their studies on the Aschoff body found in the interstices of the myocardial bundles They referred to this lesion as the myocardial Aschoff body regarded it as being particularly specific for rheumatic fever and did not consider that heart muscle cells are ever involved in the formation of this lesion They stated that So many authors have emphasized the dominant role played by injury to the collagen framework in the development of the Aschoff body that this can be considered to be an accepted fact' They further stated that in the case of the Aschoff body it seems fairly certain that the earliest stages consist of swelling eosinophilic metamorphosis and a certain amount of fusion of the collagen fibers with pari passu proliferation of the mesenchymal elements On the basis of their studies they suggested a classification of Aschoff bodies comprising seven types that appeared to them to represent different stages in the life cycle They further wrote that Studies on the Aschoff body very early in its development invariably disclose a swelling of the interstitial collagen fibers as the most conspicuous phenomenon' To them the most reliable histologic guide in attempting to 'fix the onset of an attack of rheumatic fever appeared to be the state of the collagen and concerning this

point they stated In common with a number of observers we were impressed with the fact that the collagen was the first to show damage in the form of swelling and the assumption of eosinophilic properties The earliest appearance of swelling was therefore taken as confirmatory evidence that we were dealing with the beginning of the cycle (70) With respect to the variable appearance of Aschoff bodies they concluded The histological structure of the lesion apparently depends upon whether the Aschoff body originates from the dense or the loose collagen on that phase of the life cycle of the lesion that is being studied and also to some extent on the individual reaction of the given case

The histologic studies cited in the foregoing portion of this section of the present communication led to the now widely accepted histopathological concept that rheumatic fever is essentially a disease of the connective tissue and they also served as the foundation for the expanded concept whereby rheumatic fever is linked and classified with certain other diseases i e periarteritis nodosa disseminated lupus erythematosus rheumatoid arthritis scleroderma dermatomyositis and other pathological conditions on an anatomical basis of presumed primary alteration of collagen and/or other intercellular connective tissue elements Terms used to link these diseases on this basis are collagen disease diffuse collagen disease and diseases of the connective tissue In accord with the concepts of Jacki Talalajew and Klinge it has been and continues to be widely assumed by many that rheumatic lesions in subcutaneous tissue tendon sheaths synovia and many other sites are very similar lesions with components like those in the so called Aschoff bodies in the heart Furthermore it is believed by many that in the myocardium damage to muscle cells is only incidental to connective tissue alterations and it is very widely believed that muscle cells are not involved in the formation of the so called Aschoff bodies Talalajew and Klinge considered that the characteristic cellular elements in the so called Aschoff bodies are proliferated connective tissue cells that are only secondary to a basic connective tissue change In agreement with this concept Bennett (14) in 1951 wrote as follows concerning the so-called Aschoff body

There are two essential components to it One is change in connective tissue the so called fibrinoid change and the other is the cellular response And Robbins (151) concerning the tissue changes in rheumatic fever has recently written as follows The specific lesion is known as the Aschoff body which is a microscopic focus of fibrinoid degeneration and granulomatous inflammation Baggenstoss and Saphir (9) also very closely following the concept of Talalajew and Klinge have recently stated their interpretation of the early stage of Aschoff body formation as being swelling edema, and fibrinoid degeneration of collagen and of the second or granulomatous stage (Aschoff body) as representing proliferation of connective tissue cells in reaction to the primary connective tissue injury

McEwen (117) in 1952 from study of supravitally stained scrapings of subcutaneous nodules in patients with rheumatic fever concluded that the predominant cells he observed in the scrapings represented rheumatic granuloma cells that arose from undifferentiated mesenchymal elements of loose connective tissue although he considered it possible that they arose in some instances from endothelial cells He further wrote Since there is little doubt that the subcutaneous nodules are pathologically identical with rheumatic granulomata elsewhere in the body these conclusions are considered applicable also to the Aschoff body cells of the myocardial submiliary nodules In contrast Saphir and Wile (162) at that time reemphasized the morphological differences between the Aschoff body and the subcutaneous nodule and stated 'We have used the term Aschoff body exclusively for the specific lesion found in the myocardium and Saphir (160) has recently written Subcutaneous nodules and nodules in the synovialis should never be confused with Aschoff bodies With respect to drawing conculsions about Aschoff bodies from study of subcutaneous nodules Gross and Ehrlich (69) stated Certainly the subcutaneous nodule presents a histological appearance that is different from that of the Aschoff body and apparently lacks the clear cut specificity of the latter They further stated that The Aschoff body occurring in the heart should be considered apart from the corresponding rheumatic lesions found in other tissues such as skin diaphragm tendinous insertions and so on inasmuch as the myocardial lesions present specific characteristics that are either lacking in the other sites or have been insuf

ficiently studied as yet ' The pre ent author's opinion is in agreement with tho e here cited of Fahr (49), Symmers (177) Graff (64) Saphir (160) and Gro s and Ehrlich (69) that there are clear and important morphological differ ences between A choff bodies and subcutaneous nodules

Gro s and Ehrlich (70) concluded in 1934 that their histopathological interpretation of the life cycle of myocardial A choff bodies of rheu matic fever in the last analy is, must await confirmation by the hitherto unsucce sful trans mi ion of this disea e to animals

V Experimental Induction of Myocardial Lesions Closely Resembling Those of Active Rheumatic Heart Disease Special Reference to Aschoff Bodies

A *Historical Background for the Experiments* Since the last quarter of the past century many efforts have been made to produce in ani mals cardiac le ions like tho e characteristic of rheumatic heart disease in the hope of acquir ing important knowledge of the etiology and pathogenesis of this disease A review of tho e efforts up to 1952 has been reported by the author (124 a) At least as long as 150 years ago some phy icians commented on an as oci ation between sore throat and acute articular rheumati m In 1805 Haygarth (74) mentioned cynanche as a not uncommon antecedent of attacks of rheumatic fever With the rise of the science of bacteriology in the last quarter of the 19th century numerous efforts were made to identify microorganisms as the cau e of this disea e Klebs (88) in 1878 having attempted to differentiate rheumatic valvular disease from malignant ulcerative endocarditis stated that he had observed cocci (monads) in valves in cases of acute rheumatic valvulitis Fowler (52) in 1880 reported 20 well documented ca es in which not only first attacks of acute rheumatism but in ome second attacks as well were pre ceded by tonsillitis or pharyngitis He stated that about 80% of the many cases of rheumatic fever which he had observed were preceded by symptoms of throat infection at an interval varying from a few days to a month Mantle (115) in 1886 reported recovery of diplococci and short bacilli from joint fluid and blood of patients with rheumatic fever

Apparently the first attempt to satisfy the criteria in the Henle-Koch po tulates in trying to prove a bacterial etiology of rheumatic fever was that of Popova (135) in 1887 This investi gator inoculated culture medium with blood from a patient with rheumatic fever, and re ported that growth of micrococci resulted and that the intravenous inoculation of the e micro-organisms in rabbits was followed by the de velopment of arthritis, pericarditis and endo carditis from which lesions the micrococci could be cultivated In 1899 Westphal et al (200) and Poynton and Paine (143) independently reported that with diplococci isolated from blood and tissues of patients with rheumatic fever they were able to induce in animals one or more of the following arthritis endocarditis and peri carditis Cole (34) in 1904 reported that lesions in joints and heart could be produced in ani mals following intravenous injection with vari ous streptococci from various human ources other than patients with rheumatic fever Schottmüller (165) described in 1903 a blood agar technique for differentiating hemolytic from non hemolytic streptococci and in 1915 Smith and Brown (167) distinguished between beta hemolytic and alpha or viridans strepto cocci by use of blood agar By this time there had accumulated a large number of reports of bacteremia due to viridans beta hemolytic and other streptococci in rheumatic fever patients and viridans streptococci had been reported to occur in blood and lesions of rheumatic fever patients far more frequently than other strepto-cocci Yet Swift and Kinsella (176) reported in 1917 that from acutely involved joints in patients with rheumatic fever the cultures made by them uniformly showed no bacteria They re ported the occurrence of viridans or non hemo-lytic streptococci in blood cultures from le s than 10% of the many rheumatic patients studied by them Such streptococci were recovered from valvular lesions in 3 out of 6 fatal cases of rheumatic fever and hemolytic streptococci were obtained from culture of an affected valve in 1 of these fatal ca es

In 1901 Menzer (121) suggested that acute rheumatism develops in certain individuals who becau e of hereditary or acquired condition react in a special way to infection with various microorganisms especially pathogenic strepto-cocci in the mouth Schick (163) in 1907 sug gested that the *Nachkrankheiten* of scarlet fever including migratory polyarthritis and heart di ease are allergic reactions Weintraud

(197) in 1913 impressed by the clinical resemblance of the polyarthritis of rheumatic fever and that of serum disease suggested the following hypothesis for the pathogenesis of rheumatic fever The disease exhibits an individual reaction of the organism not to primary bacterial invasion or bacterial toxins but rather a kind of anaphylatic reaction due to a secondary allergic condition caused by infection The work of the Dicks (42) and of Dochez and associates (43) reported in 1923–24 convincingly demonstrated the causative role of beta hemolytic streptococci in scarlet fever By this time it had been shown (39) that the heart disease that follows in the wake of scarlet fever with tonsillitis or pharyngitis is histologically identical with rheumatic heart disease which had itself for many years been observed to follow tonsillitis or pharyngitis *Hector (75) after clinical* study of the effects of scarlet fever on numerous rheumatic subjects reported in 1926 that the almost invariable result of scarlet fever upon a heart already damaged by rheumatism is a rekindling of the old trouble which in some cases had been quiescent for a considerable period (in case 6 for 20 years) In the same year a milk borne epidemic of sore throat (angina) caused by hemolytic streptococci involved about 2500 inhabitants of Kolding Denmark Of 840 patients under medical treatment 30 were observed to develop rheumatic fever late in the course of the epidemic (103) In 1925–26 Swift (175) and Bezançon and Weil (17) independently drew attention to the similarity of change with passage of time of the recurring manifestations of disease in tuberculosis syphilis and rheumatic fever and they believed that allergy plays an important role in these changes The analogies between rheumatic fever and serum disease remained largely on a clinical basis until Klinge and associates (85 92 187) in 1929–34 directed attention to histopathological resemblances in some of the lesions induced by them in rabbits by repeated injections of foreign serum and some of those described by them in cases of rheumatic fever Renewed interest in attempting to elucidate the pathogenesis of rheumatic fever by production of lesions in rabbits by intravenous injections of horse serum was subsequently greatly stimulated by the experiments of Rich and Gregory (149) in 1943–44

From study of first attacks and recurrences of rheumatic fever in children Schlesinger (164) suggested in 1930 that repeated infection with streptococci may be important to sensitize the body adequately enough for the development of rheumatic fever In the following year Coburn (32) submitted strong epidemiologic and bacteriologic evidence that hemolytic streptococci among all microorganisms are uniquely causative of the infections that are followed by rheumatic fever In the succeeding year Todd (184) reported a method for titrating antibodies in the serum against a streptolysin of hemolytic streptococci This investigator (185) and Coburn and Pauli (33) found that a consistent increase in titer of antibodies to streptolysin O occurs in the blood after infection by hemolytic streptococci They found this increased titer to occur similarly after infections with hemolytic *streptococci and after such infections that were* followed by rheumatic fever They found that the titer in rheumatic subjects with inactive disease was usually normal or slightly elevated and they further reported a close relation between occurrence of increase in titer and the clinical manifestations of rheumatic activity

The work of Lancefield (101) and of Griffith (68) made possible a clear serological differentiation between strains of hemolytic streptococci Lancefield (99) reported in 1933 that strains of these microorganisms can be differentiated serologically by means of precipitin reactions into sharply defined groups which bear a definite relation to the animal source of the cultures Thus group A was found to comprise chiefly strains of human origin Group A streptococci can be further divided into specific types on the basis of serologically distinct type specific M proteins (Lancefield—98) Lancefield and associates (100) demonstrated both passive and active type specific immunity to group A streptococcal infections in mice

That the character of the response of children to hemolytic streptococcal infection changes toward localization with age and with successive infections was emphasized by Powers and associates (13) and because this trend toward localization resembles in some respects comparable phenomena in tuberculosis they introduced the term streptococcosis Kuttner and Lennert (97) after studies made over a 6 year period reported in 1944 that each successive attack of group A streptococcal pharyngitis in a given individual had always been observed by them

to be due to microorganisms of a serological type different from that causing preceding infection suggesting that type specific immunity was operative in streptococcal infections in man In the following year Rantz Boisvert, and Spink (146) reported observations which suggested that reinfection with group A streptococci of different types may be important to the development of rheumatic fever Watson Rothbard and Swift (195) demonstrated active type-specific immunity to group A streptococci in monkeys that were inoculated intranasally

That rheumatic cardiac lesions in particular valvular lesions are attended by, if not the direct result of invasion of the tissues by group A streptococci was suggested by the reports of Green (66) Collis (35), and Thomson and Innes (181) on cultures at autopsy of heart valves of patients who died with rheumatic fever In these three studies taken together recovery of beta hemolytic streptococci was reported from one or more affected heart valves of 24 of the total of 36 patients whose valves were cultured This view is not supported, however by results of the following studies Swift and Kinsella (176) obtained hemolytic streptococci from an affected valve in only one out of 6 fatal cases of rheumatic fever in which the heart valves were cultured, Angevine Rothbard and Cecil (2) did not obtain hemolytic streptococci in cultures of the valves in 5 fatal cases of rheumatic fever and Klein (89) did not obtain hemolytic streptococci in cultures of valves of many patients who died with endocarditis of several forms, including rheumatic valvulitis Furthermore Watson Hirst and Lancefield (194) used strict aseptic surgical technique during post mortem examination of 4 patients ranging in age from 3 to 13 years who died with acute rheumatic heart disease in pointed effort to culture group A streptococci from the heart valves of these patients All heart valves in these 4 cases were cultured but no microorganisms were obtained Grossly visible verrucae were present on the mitral valve in all 4 cases, on the aortic valve in 2 cases and on the tricuspid valve in 1 case When they did not observe strict aseptic surgical technique in cultures of 28 heart valves of 7 other fatal cases of rheumatic fever ranging in age from 6 to 18 years they isolated hemolytic streptococci from cultures of only 2 valves both of which showed grossly visible verrucae however among these 7 patients 14 other valves showed grossly visible verrucae, but hemolytic streptococci were not obtained in cultures from them The results of this study appear to provide good evidence that the occurrence of rheumatic valvulitis is not dependent on the presence of streptococci in the valvular tissue

B *Experimental Induction of Myocardial Lesions, Closely Resembling Those of Active Rheumatic Heart Disease, by Repeated Focal Infections With Group A Streptococci* —In an effort to experimentally induce cardiac lesions like those in rheumatic heart disease the author and Dr Homer F Swift began a series of long term experiments in 1946 at the Rockefeller Institute These experiments are continuing New Zealand red and hare brown rabbits of the random stock of the Rockefeller Institute were initially employed Subsequently we have used rabbits of a stock specially bred as outlined in the section on *Purpose of This Communication* We selected group A streptococci isolated from patients that had undergone many mouse passages (intraperitoneal) and some strains in addition were passed intravenously through many rabbits The streptococci have grown in matt or mucoid colonies on rabbit blood agar and produced relatively large amounts of M protein in Todd Hewitt broth made with neo peptone In the initial experiments 15 to 20 hour broth cultures were serially diluted in tenfold steps with Todd Hewitt broth In subsequent experiments the dilutions have been made with freshly filtered Tyrode s solution to which 1% normal rabbit serum is added Because it seemed impractical to attempt to produce suitably sized repeated focal infections in the throats of rabbits and impossible to follow carefully the local response to such infections in that site repeated focal cutaneous infection each with streptococci of different serological types, have been set up in closely clipped right and left gluteal or lumbar skin at approximately monthly intervals Inocula, given intracutaneously in 0 1 cc volume have contained between 10^{-4} and 10^{-8} cc of the original culture A period of 2 to 4 months has been allowed to elapse before the last or 'challenge infection

Earlier results of these experiments have been reported in detail (123 127, 128) Summarized briefly they were as follows After sustaining multiple successive focal cutaneous infection

some rabbits sickened Among these some were allowed to recover (category A) and were subsequently reinfected focally a portion were sacrificed within 10–15 days following the last infection (category B) while exhibiting definite symptoms of illness leukocytosis and erythrocyte sedimentation rates that were higher sometimes markedly than occurred in controls simultaneously infected with the same streptococci a few developed severe and fatal illness after repeated infections (category C) whereas control animals undergoing their first infections with the same streptococci usually survived A very few here designated C-1 in category C died within 2–5 days after the last infection (even though a very large majority of normal controls survived infection with the same streptococci) and in all except one of these rapidly fatal cases streptococcal bacteremia was established Among the rabbits in category C a few here designated C-2 that died between 6 and 14 days after the last of repeated infections developed streptococcal bacteremia but in the remainder here designated category C-3 of the animals that died between 6 and 14 days after the last infection streptococci could not be cultured from the blood either before or shortly after death although streptococci were systematically sought for in blood cultures in every animal There were found in the hearts of some animals in categories B and C fresh valvular myocardial and coronary arterial lesions closely resembling those of active rheumatic heart disease and these lesions occurred in various combinations Myocardial lesions closely resembling Aschoff bodies and fresh vascular lesions were found in the animals in categories B C-2 and C-3 that lived longer than those animals in category C-1 and these myocardial and vascular lesions and those of human rheumatic heart disease differ in several important respects from those of experimental and human serum disease (128) Myocardial scarring and healed arterial lesions like those of rheumatic heart disease were found in the hearts of some rabbits that sickened and also in the hearts of other rabbits that were sacrificed after repeated infections but without signs or symptoms of active disease at the time of sacrifice

In the present communication further evidence is submitted of the close resemblance between myocardial lesions in active rheumatic heart disease and those induced by repeated focal infections with group A streptococci in rabbits with special reference to Aschoff bodies as shown in Figs 1–18 49–54 66 69 148 149 151 and 152 Among rabbits of random stock we have not found these lesions in 1) very numerous normal control rabbits 2) many that died or were sacrificed a few days to several weeks after one infection 3) many immunized by intravenous route with killed group A streptococci or 4) many that died or were sacrificed a few days to several weeks after receiving by intravenous route a large inoculum of living group A streptococci of one of several different serological types Furthermore among the very many rabbits of *random* stock that have been repeatedly infected focally by us with group A streptococci only a small to moderate proportion have shown rheumatic type lesions of blood vessels and only a few have shown myocardial lesions resembling Aschoff bodies and valvular lesions like those in acute rheumatic fever However among a strain of rabbits *specially bred* as outlined earlier in this communication the incidence of myocardial and of valvular lesions following repeated focal infections with group A streptococci is considerably greater These findings will be the subject of a future communication

Our investigations thus indicate that important to the pathogenesis of rheumatic heart disease is a particular altered host reactivity to infection with group A streptococci that is induced by previous infection with these microorganisms The results of these experiments are in harmony with the fact that rheumatic heart disease occurs in nature in only a small proportion of the very many in the random human population who experience repeated focal infections with group A streptococci Furthermore the results of these experiments appear to satisfy the postulates that Opie (133) suggested should be fulfilled before one could attribute an important role to hypersensitivity in causation of a disease In 1936 Opie wrote as follows The evidence assembled to show that allergy is essential to the production of certain diseases for example rheumatic fever glomerular nephritis and lobar pneumonia is inconclusive even though it is evident that allergic phenomena modify their course It would be unwise to attempt the elaboration of postulates defining allergic disease after the model of Koch s postulates concerning the causation of infectious diseases

Nevertheless certain conditions mu t be fulfilled before the allergic origin of a disea e can be established It must be shown that sen itiza tion precedes the production of the disease by its inciting agent This inciting agent must be capable of reproducing the disease ex perimentally in sensitized animals The inciting agent must be demonstrable in such relation to the human disea e that its symptomatology and lesions are explainable Though much sug gestive evidence has been collected the e con ditions have not as yet been fulfilled for any infectious di ca_e In the ca_e of our experi ments we infected animals with microorganisms of the species causative of the nasopharyngeal infections that o commonly precede attacks of rheumatic fever That sensitization preceded development of the rabbit myocardial lesions is indicated by the fact that these lesions oc curred only after repeated focal infections As in patients who develop rheumatic fever so too in the rabbits of these experiments the strepto coccal infection was focalized distant from the heart and as in human rheumatic myocardial lesions o too in the experimentally induced myocardial le ions streptococci could not be demonstrated

Several students of rheumatic fever have not accepted our evidence of the clo e resem blance between the rabbit and human lesions and Saphir (159) has been insistently critical of our evidence In regard to A choff bodies found in patients who died with acute rheu matic heart disea e that were illustrated by us and submitted to demonstrate the close re semblance of these human lesions to those in duced by us in rabbits (123) Saphir and Lan gendorf (161) stated that in our opinion the e mu cular lesions are not A_choff bodies since they are at variance with the criteria as to what constitutes a typical Aschoff body While it is possible as Murphy showed that such lesions in the myocardium involving muscle fibers can be reproduced experimentally a typical Aschoff body as yet has not been reduplicated in an experimental animal The importance of cla_sify ing structures as A choff bodies only if they fulfill the criteria cannot be overstre_ed If the e criteria as to what constitutes a specific rheumatic nodule or an Aschoff body were re laxed to include parenchymatous nodules with centers of necrotic muscle surrounded by cells like those u_ually found in an A_choff body then of course, the lesions described here could be designated as A_choff bodies If such a broadened criterion were accepted the mor phologic diagnosis of rheumatic carditis would lose its specificity for the only pathognomonic feature the morphologist now has for diagnosis would have been acrificed

The use of proper morphologic criteria is es ential in histopathological studies From the evidence at hand it appears to the pre ent author that the morphologic criteria employed by Saphir as to what does or does not constitute the true Aschoff body are not only unduly arbitrary but they fail to take into account at all the involvement of mu cle cells which our evidence ubmitted previou ly (123 126) and here shows is es_ential for the development of these and other rheumatic lesions of the myo cardium Saphir (159) has recently written a brief review of attempts to experimentally pro- duce in animal myocardial lesions like tho e characteri tic of rheumatic heart disease and in this review he rejects the evidence that we had previously submitted (123 128) to show not only the clo e resemblance between human Aschoff bodies and myocardial lesions induced by us in rabbits but al o to demonstrate the es_ential involvement of mu cle cells in Aschoff bodies In beginning this review Saphir states The following discourse is not unbiased rather it reflects the experience gained from many ob- servations Since in the course of reiteration of his rejection of our evidence he (9) has written that scrutiny of relevent photomicro- graphs for comparison with the typical body in the granulomatous stage should be revealing to the unbiased ob_erver it would appear pertinent to refer to the judgement of patholo- gists who are unbiased in this regard and yet have had con iderable experience in the study of the pathology of rheumatic heart di ea e

Klemperer (90) in pointed respect both to the rabbit lesions produced by us and to the criteria of Saphir as to what does or does not constitute the o-called A choff bodies recently stated that I cannot skip over the astonishing imilarity between the experimental lesions and the A choff bodies in the human simply becau e the latter have been arbitrarily defined Con cerning evidence previously submitted by us (123 127 128) Klemperer further wrote I have very carefully studied his plates that com pare the lesions experimentally induced by him

with those of human myocarditis I have spent considerable time reviewing the classic publications of Gross and Ehrlich and the most recent articles of Saphir and Langendorf and of Ruebner I have studied in these last months many cases of rheumatic myocarditis from our files and I have become amazed by the great similarity of the human lesions and those that have been produced by Dr Murphy in the rabbit

Concerning our experimental studies referred to here Harrison (72) has written as follows

Recently Murphy and Swift (1949–50) have attempted to reproduce rheumatism in rabbits by following what they believe to be the usual course of events in man They assumed that rheumatism in man followed repeated infections with Group A beta hemolytic streptococci but they argued that in all probability succeeding infections were caused by different serological types They therefore induced repeated infections in rabbits by giving carefully graded small intradermal doses of Group A streptococci of different types which would produce infections well within the capacity of the animal to overcome These infections were repeated at about monthly intervals over six months or a year They noted that if they gave the injections at different sites the later ones produced a more violent local reaction than the early ones suggesting the development of an increased sensitivity After a variable number of injections some of their rabbits became ill with dyspnoea leukocytosis rapid irregular pulse and raised sedimentation rate and died in 4–14 days In these rabbits they found endocardial and myocardial lesions which bear a striking histological and cytological resemblance to those of acute rheumatism Furthermore they did not find evidence of the polyarteritis which so often accompanies the cardiac lesions in animals made hypersensitive to foreign serum On the other hand arterial lesions were produced which closely resembled those of naturally occurring rheumatic arteritis The interest of this work lies not only in the remarkable similarity of the lesions to those of human rheumatism but in the fact that the mode of production is similar to that which is believed to operate in human cases It is obviously hazardous to apply the results of animal experiments directly to man but there now seems to be good evidence for the belief that acute rheumatism is an expression of altered sensitivity to repeated infections by Group A streptococci of varying serological types One question still remains unanswered Recurrent Group A streptococcal tonsillitis is an excessively common experience at all ages yet the proportion of those susceptible to this recurrent infection who develop recurrent carditis is inexplicably small The same low incidence of cardiac lesions was found by Murphy and Swift in experimental animals

VI Evidence that Aschoff Bodies are Lesions of Muscle Cells

A Evidence from Experimental Induction of Myocardial Lesions Closely Resembling Aschoff Bodies—In contrast with the generally accepted concept that all Aschoff bodies represent primary injury to collagen and/or other connective tissue components to which nonmyogenic cellular elements react our comparative studies on the histopathogenesis of lesions of Aschoff body type induced experimentally by repeated focal group A streptococcal infections in rabbits and of Aschoff bodies in a very large number of patients have revealed the following Aschoff bodies originate and evolve from rheumatic injury to heart muscle cells The mono multi and nonnucleated structures characteristic of these lesions are of two types 1) damaged muscle cells or fragments thereof (Figs 28–45 64–90 154–162) and 2) syncytial masses of myogenic origin that proliferate from inside the sarcolemma in the tracks of disintegrated muscle cells (Figs 7 8 10–18 52 53 57 and 59) and these syncytial masses usually basophilic appear in the beginning to represent an attempt at regeneration of heart muscle cells Mono- or multinucleated fragments of myofibers are very commonly mistaken for histiocytes or other nonmyogenic mesenchymal cells and *nonnucleated* eosinophilic sarcoplasmic fragments of myofibers (Figs 10–27 48–60 147 160 and 162) that have completely lost their striations are usually erroneously called swollen collagen fibrinoid collagen or fibrinoid In later stages in the evolution of Aschoff bodies necrotic myofibers are commonly replaced by thick, new collagen fibers and the formation of this collagen in the scarring process commonly masks the evidence in these lesions of the earlier primary damage to myofibers In patients who die after repeated attacks of rheumatic fever myofiber fragments near arteries or at a distance from arteries may

be obscured by collagen that has been laid down either during the previous attacks or in the course of the final ones

B *Origin of Interstitial Myocardial Aschoff Bodies From Heart Muscle Cells in Bundles Between or Among Other (Often Larger) Bundles of Muscle*—Aschoff bodies have been repeatedly described as occurring in interstices between bundles of myofibers The word interstitial in description of rheumatic myocardial lesions was used by Goodhart in 1879 in referring to "interstitial cell growth around the vessels and between the muscular fasciculi", by Cadet de Gassicourt in 1887 in reference to "proliferation of cellular interstitial growth", by Krehl in 1889 who referred to "interstitial myocarditis", by Aschoff in 1904 who referred to the specific lesions as "interstitial myocarditis" and recently by Baggenstoss and Saphir who refer to the Aschoff body as representing "focal interstitial myocarditis"

In accord with his concept that all characteristic rheumatic lesions essentially represent reaction of connective tissue to injury Talalajew stated that "in the case of the myocardial localization of the process the exudative-degenerative moment is usually weak, and the process appears to begin with the primary cellular proliferation which is in accord with the views of Aschoff" Concerning the histologic characteristics of rheumatic cardiac injury Baggenstoss and Saphir have recently stated that "attention has been concentrated primarily on the proliferative and exudative phase of the inflammatory reaction to the neglect of what is now widely accepted as the primary injury to the connective tissue The lack of study of this phase of the inflammatory process is understandable because it is relatively poorly developed in the myocardial lesions and often obscured by the exudative and proliferative processes" Why I would like to ask should the hypothetical "exudative-degenerative moment" of connective tissue change referred to by Talalajew be weaker in the myocardium than elsewhere or why should the hypothetical "primary injury to the connective tissue" be "relatively poorly developed in the myocardial lesions" (Baggenstoss and Saphir) as compared with rheumatic lesions elsewhere? There is no lack of collagenous connective tissue in the myocardium to explain a hypothetical weak or poorly developed primary reaction in connective tissue here as compared with such a hypothetical reaction in connective tissue elsewhere in the heart or in other parts of the body With respect to this point Gross and Ehrlich (69) wrote as follows "While a considerable concentration of collagen is found around blood vessels and in the subendocardium its distribution in the heart considered as a whole is not so widespread around the vascular bed and subendocardium as it is in the interstitial tissue between the muscle bundles"

In the reports that I have read of many pathologists since 1879 who have stressed the occurrence of Aschoff bodies in the "interstitium" between large bundles of myofibers I have been astonished at the consistent failure to take into account the occurrence of myofibers few in number or in small or larger bundles between or among other bundles of myofibers Quite clearly myofibers occur in small aggregates or bundles and in larger bundles *between* or *among* other bundles of myofibers (Figs 19–27 70–74 76 77, 79–81) Usually by the time the pathologist observes the lesions in rheumatic heart disease involved interstitial muscle between or among other muscle has been destroyed or it has been so altered that it is no longer recognizable as muscle in the myocardial lesions Figs 2 6 13, 19–27 55 74 80 and 81 illustrate the origin of so-called "interstitial" Aschoff bodies from cardiac muscle fibers of bundles between larger bundles of muscle fibers And Figs 48, 50 54 55 73 76 77, 79 and 162 further indicate how Aschoff bodies, derived from bundles of cardiac myofibers among other bundles will themselves eventually be converted in the scarring process into "interstitial" areas of connective tissue between intact contiguous bundles of myofibers When single myofibers (Figs 28–31 34–36 70 72 156 and 161) or myofibers in small or larger aggregates (Figs 2 4, 6 8 25 27, 73 74 76 77 79–81 157–160 and 162) between or among (other) bundles of myofibers become damaged beyond recognition in the formation of the structures characteristic of rheumatic disease of the myocardium it is understandable how advocates of the generally accepted connective tissue concept of the origin of these lesions fail to take into account the essential involvement of myofibers for recognizable fragments of the myofibers are only found in the early stage of development of these rheumatic lesions In later stages the unrecognizable myogenic elements are

often further obscured by collagen laid down in scarring

C *Origin of Aschoff Bodies From Heart Muscle Cells Close to Blood Vessels* —Aschoff bodies have al o been repeatedly described as occurring very near arteries (Figs 4 75 and 78) I have repeatedly observed that individual as well as small and larger aggregates of myofibers occur in very clo e proximity to blood vessels Indeed heart muscle fibers sometimes occur so close to the media of myocardial vessels that it is difficult to see vascular adventitia between Figs 16 37–45 75 and 78 illustrate the occurrence of muscle cells close to blood vessels and the origin of the cellular elements so characteristic of Aschoff bodies from muscle cells so located When myofibers in these sites become damaged beyond recognition (Figs 75 and 78) in the formation of rheumatic lesions it is understandable how one may fail to take into account the essential involvement of myofibers near blood ves els for recognizable fragments of the paravascular myofibers may only be evident in the earliest stage of the Aschoff body formation The end result of rheumatic damage to paravascular muscle cells in the myocardium is replacement of these muscle cells by often thick collagen fibers of scar

D *Connective Tissue in Aschoff Bodies Some of The Reasons for The Common Misinterpretation That Aschoff Bodies Are Non-myogenic Lesions Derived From Connective Tissue Elements* In Aschoff bodies previously illustrated and submitted by us as evidence of the myogenic origin of these lesions (123 126) there was neither fibrinoid alteration of collagen fibers nor fibrinoid material between collagen fibers and although some thick collagen was evident in some lesions the collagen in the majority of lesions was thin and stained as normal collagen In the present communication there are submitted many more illustrations of Aschoff bodies in which the connective tissue appears normal In the Aschoff bodies in Figs 33 73–81 and 85–90 the connective tissue is normal the collagen delicate As previously mentioned in the first part of this section Figs 10–21 23 24 27 33 48 50 52 54 55 57 59 60 77 80 81 147 160 and 162 illustrate sarcoplasmic fragments of myofibers that have completely lost their striations Such sarcoplasmic fragments are very often erroneou ly referred to as swollen fragmented clumped or fused collagen fibrinoid collagen , or fibrinoid Figs 10–12 and 17 from a rabbit and Figs 15 and 18 from humans show central cores of sarcoplasm in intimate connection with myogenic multinucleated masses The lesion in Fig 16 from a human is strikingly like that in Fig 17 from the rabbit and the changes in Fig 13 from a human are strikingly like those in Fig 10 from a rabbit Likewise the syncytial multinucleated structure at the top of Fig 14 from a human bears very striking re emblance to that in Fig 11 from a rabbit Figs 10–18 illustrate what in my view is probably a limited attempt at regeneration of cardiac muscle cells in both the experimental lesions and the human rheumatic lesions and Fig 52 from a human and Fig 53 from a rabbit illustrate this same point Taken alone the lesions in Figs 50 52 54 57 59 and 60 from humans might be interpreted by many as showing a central core of fibrinoid however when studied together with the other pictures of human and rabbit lesions of muscle cells in these two plates (Figs 46–63) and with Figs 10–18 it hould appear obvious that these are lesions with a central core of sarcoplasm Figs 52 and 59 are sections of the same lesion

In the myocardium of patients with active rheumatic heart disease there may occur focal areas of thick collagen fibers some of which may with certain techniques stain like fibrin intermingled with small and large cellular elements In interpreting the significance of such changes the following observations are pertinent 1) Some collagen fibers in normal tissues may take the same stain as fibrin with various staining techniques 2) in the myocardium of patients who have experienced attacks of rheumatic fever many years before succumbing to [illegible] cirrhosis of the liver associated with heavy intake of alcohol over many years I have found that ome of the thick collagen fibers in focal myocardial scars stained like fibrin in the complete absence of cellular reaction Likewise, at the time of death of these patients there was no clinical or histological evidence of [illegible] disease in any of the many [illegible] the collagen in the scarred [illegible] of these patients al o stained like fibrin The patients just referred to had in the [illegible] as having Laennec s cirrhosis by a medical [illegible] pointedly concerned [illegible] the study of [illegible] disease and although these patients had [illegible] of attacks of rheumatic fever many years [illegible]

death there were no clinical or histological findings to suggest that the patients had ever been in cardiac failure, and the cirrhosis, therefore was *not related to congestive heart failure* The observations cited just above when taken together indicate that in evaluation of the significance of thick collagen fibers, some of which may stain like fibrin, in the hearts of patients *with inactive or active rheumatic heart disease*, the following must be considered as a likely explanation the thick collagen fibers were probably laid down in scarring during previous rheumatic attacks and/or in the course of the final attack

In connection with this point it is pertinent to refer to the detailed morphologic studies of Gross and Ehrlich (69, 70) who attempted to *trace the life cycle of myocardial Aschoff bodies* One of the seven structural configurations of Aschoff bodies which they described is the small cell coronal type which, according to these authors comprise a central mass of swollen collagen surrounded by a mantle of small basophilic cells *They believed that this lesion represents* a very early stage of rheumatic damage yet they failed to find this lesion in any of the patients who died during a *first* attack of rheumatic fever This lesion was found by them only in those cases in which more than one attack of rheumatic fever had occurred If as they maintained this lesion really represents one of the two earliest stages of Aschoff bodies one would certainly expect to find this lesion in a *first* attack rather than only after repeated attacks In my view there are two possibilities that best explain the occurrence of the so called small cell coronal type Aschoff body 1) The "swollen collagen may represent thick collagen laid down during previous attacks or in the course of the final attack and 2) the central core in some of these lesions is not collagen it is *sarcoplasm of muscle that has disintegrated as shown* in Figs 50 54, 57, 59 and 60 Indeed, the lesion in Fig 60 has an almost identical appearance to that in Fig 1 in a paper by Gross and Ehrlich (69) illustrated as their example of the small cell coronal Aschoff body

In active rheumatic heart disease foci of strands of stringy, ramifying sometimes interlacing material, that stain like fibrin are occasionally found in the myocardium This material may very well be fibrin itself that has passed from the blood through small vessels that are often injured in rheumatic fever, and such material is sometimes found in valves and not uncommonly in pericardium, subcutaneous nodules on and beneath the lining cells of synovial membranes, and in other tissues That Aschoff bodies and experimental lesions of Aschoff body type can occur, as illustrated previously (123, 126) in the absence of fibrinoid and in the absence of strands of stringy ramifying material that stain like fibrin is further *clearly* demonstrated here in Figs 1-5 33, 73-90 157, and 159

In this connection it is pertinent that Aschoff (5), in 1939 after study of these lesions over a period of thirty five years published illustrations in color of several characteristic fresh Aschoff bodies in the myocardium of a six year old child After commenting on the normal appearance of the connective tissue in the *Aschoff bodies in this case*, he further wrote in criticism of the hypothesis concerning fibrinoid in rheumatic lesions Despite the cellular overgrowth which has caused the formation of the nodules there is no trace of a fibrinoid degeneration of *the ground substance' And in reference to myo*cardial Aschoff bodies in general he concluded

It is in no way essential that the formation of the richly cellular nodules should be preceded by fibrinoid degeneration of the ground substance On the basis of my own studies carried out intensively in the past ten consecutive years, of a very large number of cases of active rheumatic heart disease I am in complete agreement with Aschoff on this point and in obvious disagreement with the conclusions of Talalajew (178) Klinge (91) and the many who have followed them (9 23 76, 151 156 159 179, 193)

*The lesions in the myocardium known gener*ally as Aschoff bodies, have in my opinion characteristic features that clearly distinguish them not only from rheumatic lesions outside the heart but also from the great bulk of rheumatic lesions in cardiac valves and sub-pericardial tissue This distinction in my view, is based on the primary and marked damage to heart muscle cells that results *in the two types of cell masses that I* have previously (123 126) and more extensively here described and illustrated In this connection it is pertinent to mention that Aschoff (5) in 1939 placed particular, and to me distinguishing emphasis *on the specific rheumatic lesions in the* myocardium as compared with rheumatic lesions elsewhere Aschoff wrote 'Having surveyed the world literature I am still convinced

that rheumatic nodules *as seen in the heart muscle* (present author's italics), are specific to this rheumatic disease, and he further stated "As a result of my experience I can state emphatically that the rheumatic nodules *which appear in the myocardium* (present author's italics) are specific to the Bouillaud Graff disease (rheumatic fever)"

The occurrence of heart muscle cells in cardiac valves (Figs 109–116) and among fat cells in sub-epicardial tissue (Fig 153) is discussed in section VI E and the occurrence of smooth muscle cells in atrial appendage and cardiac valves (Figs 91–108) is discussed in sections VII A and B

E *Occurrence of (Striated) Heart Muscle Cells in Cardiac Valves and Among Fat Cells in Sub epicardial Tissue*—One argument that has been employed by some investigators (156 193) against evidence of the myogenic origin of Aschoff bodies is to use the words of one critic that "Aschoff cells are often found in situations where there is no muscle i e in the sub-epicardial tissue and in the valves" (156) Evidence submitted with the present communication demonstrates that this criticism is not valid All auriculo ventricular valve cusps have inserted into them a wedge of myocardium that extends for greater or lesser distances down the valve Fig 110 illustrates this point in a human mitral valve and Figs 109 and 111 illustrate this in rabbit tricuspid and mitral valves Figs 112–114 illustrate the occurrence of considerable striated heart muscle half way between the mitral sulcus and the tip of a mitral valve in a nine year old boy who died with acute glomerulonephritis (there was no evidence of active rheumatic heart disease) Fig 115 illustrates clusters of striated heart muscle cells in the first portion of a mitral valve and Fig 116 shows considerable striated heart muscle in an extension of a wedge of striated myocardium well out into the aortic leaflet of a mitral valve Fig 117 shows striated heart muscle fibers inserted well down along and into a chorda tendinea

The occurrence of smooth muscle cells in cardiac valves illustrated in Figs 99–108 will be discussed later in this communication

Lesions resembling the myocardial Aschoff bodies have been reported in sub-epicardial tissue Coombs (39) illustrated and described in rheumatic pericarditis perivascular areas of fibrinous deposit and cellular infiltration similar to the submiliary nodule It is noteworthy that MacCallum (110) found such lesions in sub epicardial tissue but never in the parietal layer of the pericardium In rheumatic pericarditis deposits of fibrin may be misinterpreted as fibrinoid or fibrinoid degeneration of connective tissue In sites of such exudate histiocytes may be found and I have in several cases been able to identify mesothelial lining cells of the epicardium that are basophilic and have become sequestered in this exudate or in the chronic inflammatory reaction that follows And not uncommonly I have observed pseudo-glandular proliferation of these sequestered epicardial cells like that shown by Baggenstoss (8) Certainly focal acute and chronic inflammatory reactions that resemble those in valves synovia and subcutaneous nodules occur in rheumatic pericarditis But these changes should not be interpreted as Aschoff bodies On the other hand cardiac muscle fibers occurring singly in small aggregrates or in larger aggregates often appear to be isolated in sub-epicardial tissue from the body of myocardium Fig 153 shows such a cluster of heart muscle fibers among fat cells *well out in sub-epicardial tissue and connection* of this muscle to the body of myocardium beneath does not occur in this section Such aggregates very probably represent finger like or other forms of projection of myocardium which happen to be sectioned in such a way as to appear isolated in sub-epicardial tissue Rheumatic involvement of such apparently isolated heart muscle fibers could result in a myocardial Aschoff body that would *appear* to be in the sub-epicardium and isolated from the rest of the myocardium

F *Elucidation of the Myogenic Origin of Rheumatic Myocardial Lesions Including Aschoff Bodies From Findings in Human and Rabbit Skeletal Muscle*—In two cases of rheumatic fever Huzella (77) described lesions in skeletal muscle that closely resembled Aschoff bodies in the myocardium He believed that he could trace the origin of giant cells closely resembling those in Aschoff bodies from muscle cells in these lesions of skeletal muscle This has also been my experience and our findings in both human and rabbit skeletal muscle shed light on the myogenic nature of myocardial Aschoff bodies Fig 46 from skeletal muscle of a rheumatic subject and Fig 47 from skeletal muscle of a rabbit repeatedly

infected focally with group A streptococci are strikingly like the myocardial Aschoff body in Fig 48 In turn these three lesions are like those in Figs 49 and 50 Fig 55 shows an Aschoff body that would be referred to by many as interstitial This Aschoff body is derived as are the lesions in Figs 20 23 24 and 27 from the same patient from a bundle of myofibers between larger bundles In this Aschoff body the track of a disintegrated myofiber can be traced from the upper left portion to the lower right portion and in the upper portion of this track is granular sarcoplasm and in the lower portion of the track a slightly basophilic elongated mass of sarcoplasm At the top central portion of the Aschoff body is a multinucleated structure with annular arrangement of nuclei This structure is identical to those in Figs 57 and 61 from the same patient Note the striking resemblance of all these structures to that in rabbit skeletal muscle (Fig 56) which is an obviously myogenic structure with annular arrangement of myogenic nuclei around a core of sarcoplasm Note also the striking resemblance of the annular lesions in Figs 55–57 and 61 to that in Fig 59 from another patient Fig 59 and Fig 52 are sections at different levels of the same lesion Then note the striking resemblance of the myogenic lesions in rabbit skeletal muscle in Fig 58 to the human rheumatic lesion in Fig 59 Furthermore the structure with the annular arrangement of nuclei in the rheumatic lesion in Fig 63 is very strikingly like the obviously myogenic structure of the rabbit skeletal muscle in Fig 62 in which the nuclei are arranged in a ring within the sarcoplasm Fig 64 is from skeletal muscle of a rheumatic patient who died with Aschoff bodies in the myocardium That this is a myogenic lesion with basophilic sarcoplasm and proliferated myogenic nuclei is evident Fig 67 from rabbit skeletal muscle shows a very similar lesion comprising only and very obviously multinucleated fragments of a myofiber The lesions of rabbit skeletal muscle in Figs 65 and 67 show multinucleated myogenic structures that very closely resemble the human one in Fig 68 that is from the myocardium of a patient who died with active rheumatic heart disease

In my judgment the lesions of *skeletal* muscle cells here illustrated are probably not specific for the sequelae of focal infections with group A streptococci in either humans or rabbits The fact remains, however that these lesions were found in respectively patients who died with rheumatic heart disease and rabbits that markedly sickened after repeated focal infections with group A streptococci and these lesions are included in this monograph because of the aid they give in elucidating the histopathogenesis of rheumatic lesions of heart muscle cells

G *Origin of Aschoff Bodies from Heart Muscle Cells in Cardiac Atrial Appendages*—Since 1951 many reports have been published (18 28–30 41 44 47 48 83, 95 102 108 111 114 118–120 126 138 140 150 156 170 179 180 186 190) on histologic studies of left atrial appendages removed at the time of operation performed to alleviate mitral stenosis in patients who showed signs and symptoms of cardiac failure of varying severity and duration Although the very large majority were considered to show no clinical evidence of rheumatic activity at the time of the cardiac surgery a large proportion have shown specific rheumatic lesions generally referred to as Aschoff bodies in the biopsied left atrial appendage

The atrial lesions that resemble closely some Aschoff bodies in the ventricular myocardium are described by many as occurring in the endocardium of the atrium Since cardiac myofibers do not occur in the endocardium some observers have interpreted the repeated findings of Aschoff bodies in the mural endocardium of the auricular appendages (193) as evidence contrary to our evidence of the development of Aschoff bodies from injured muscle cells However my own findings have shown that such atrial Aschoff bodies (Figs 82–86 88–90) that closely resemble some of those in the ventricular myocardium (Fig 87) originate from damaged heart muscle fibers just subjacent to the subendocardial zone of smooth muscle and connective tissue (125 126) As it expands an Aschoff body developing from heart muscle cells in this area often thrusts its way toward the endocardium so that part of the Aschoff body comes to lie in the subendocardium When in those areas where the subendocardial zone is thin these myocardial Aschoff bodies in expanding come to lie close to the overlying endocardium they are commonly misinterpreted as endocardial Aschoff bodies These and other points are illustrated in Figs 82–90 and will now be discussed Fig 82 shows several Aschoff bodies in the lower portion of the picture and one at

the top center Except where the A choff bodies occur one can see that the myocardium comes very close to the endocardium and the clear inference here borne out in the other figures of this plate is that the Aschoff bodies are recent nodular defects in myocardium just below the subendocardium Fig 83 very probably represents an early stage of a small Aschoff body clearly representing focal disintegration of heart mu cle cells just subjacent to the subendocardium Collagenization of this little wound would be expected to occur and it appears to be under way Fig 84 also shows an Aschoff body derived from heart mu cle cells just subjacent to the subendocardium The connective tissue in this lesion appears normal Note the tendency of the nodule to expand toward the endocardium Fig 87 is an A choff body that illu trates the same change in the left ventricle Figs 85 and 86 are from the same ection stained successively by two methods The connective tissue appears normal in this lesion which is an Aschoff body and clearly derived from a bundle of heart muscle cells and it has expanded slightly toward the subendocardium Figs 88 and 89 are from the same section of another appendage that was stained successively by two methods The connective tissue appears normal in this lesion which is also derived from a little bundle of heart muscle cells Fig 90 very probably represents the following The atrial myocardium has been eroded or cut back by rheumatic activity and in the process A choff bodies from damaged muscle cells have formed Collagenization of the e myocardial wounds has occurred and is still underway

With re pect to the origin of rheumatic myocardial le ions von Albertini (1) was able to determine that many myocardial nodules are of myogenic origin and Ghosh (60) from study of the heart of patients who died with a clinical diagno is of acute rheumatic heart disease concluded that the pathologic changes were due mainly to degenerative and reactive phenomena on the part of the cardiac muscle cells

Rheumatic injury to those cardiac muscle fibers that are widely considered to constitute specialized conduction tissue should probably be expected to result in lesions essentially like or identical with tho e that result from rheumatic injury to other cardiac mu cle fibers Indeed there have been reported in ca es of active rheumatic heart disease alterations of heart mu cle fibers in the atrioventricular node (26) and in the atrioventricular bundle of His and left bundle branch (107a 173a) like rheumatic lesions that occur elsewhere in the myocardium Lumb and Shacklett (107a) found in the left bundle branch and illustrated an Aschoff body strikingly like tho e in Figs 2 80 and 81 in the present communication The lesions here shown in Figs 2 80 and 81 were deep in the posterior wall of the left ventricle Figs 80 and 81 are from the patient referred to in Figs 26 38 45 68 73 76 and 79

VII Disease of Smooth Muscle Cells in Rheumatic Heart Disease

A *Rheumatic Disease of Smooth Muscle Cells in the Subendocardial Tissue of The Atrium Special Reference to Lesions in Atrial Appendages That Resemble in Varying Degree Aschoff Bodies That Are Derived from Heart Muscle Cells*—With respect to specific rheumatic lesions found in the subendocardium of the atrium the fact is very often indeed usually not taken into consideration that smooth muscle cells normally occur in varying amount often in large numbers and sometimes in strata between atrial endothelium and the body of striated myocardium And in some portions of the atrium including the atrial appendage smooth muscle occurs very close to the endothelium These points are clearly illustrated in Figs 91–98 It has long been known that smooth mu cle cells in media of myocardial arteries are often damaged in rheumatic fever (87 129) and I have observed multinucleated smooth muscle cells and lesions resembling A choff bodies in the media of myocardial arteries (Figs 118–135) that will be later discussed It appears that reaction to rheumatic fever injury of smooth muscle cells in atrial subendocardial tissue (between endothelium and striated myocardium) results in focal lesions homologous with tho e here illustrated in the media of myocardial arteries and the e lesions in varying degree resemble the so-called Aschoff bodies that are derived from *heart muscle* cells Fig 91 shows a section of atrial appendage stained with phosphotungstic acid hematoxylin to illu trate that an avenue or band of smooth mu cle cells normally occurs in the subendocardium In Fig 94 just below one sees a similar avenue of smooth muscle in the

subendocardium of atrial appendage from another patient As the eyes of the viewer move down this avenue of smooth muscle, they come to a lesion that lies directly in the lower portion of this avenue and which has the same width as that of the avenue of smooth muscle This lesion is shown in higher magnification in Fig 97 and is a specific rheumatic lesion, which resembles an Aschoff body that develops from heart muscle cells Indeed, this particular lesion resembles those myocardial Aschoff bodies designated by Gross and Ehrlich (69) as being of coronal configuration

Fig 95 is from a rabbit that died 11 months after the last of 5 focal infections with group A streptococci Of considerable interest to the writer is the fact that several days after the beginning of the last focal infection this rabbit developed a cardiac systolic murmur that persisted until death of the animal Note the striking resemblance between the rabbit atrial lesions in Fig 95 and the human atrial lesions in Fig 96 that is from a patient who died with chronic active rheumatic heart disease

In Figs 92 and 93 are seen broad avenues of subendocardial smooth muscle The evidence here submitted indicates that the lesions in Figs 94–97 are lesions of smooth muscle cells MacCallum (109) described nodular rheumatic lesions sometimes curiously forced into rows between elastic fibers in atrial subendocardium It should be recalled as pointed out in the beginning of this section that smooth muscle cells occur normally in rows or strata in atrial subendocardium

The lesions of smooth muscle cells here illustrated may well be termed *specific rheumatic* lesions of smooth muscle

Von Glahn (189) described in atrial subendocardial tissue rheumatic change comprising dense infiltration with polymorphonuclear leukocytes small round cells a few plasma cells and occasional eosinophiles in association with pale cells with vesicular nuclei It would appear that this subendocardial change, very probably importantly associated with damaged smooth muscle elements is analogous to the infiltration of damaged myocardium with inflammatory cells associated with myogenic cellular elements (as shown in Fig 150) that will be discussed in section IX.B of the text

B *Rheumatic Disease of Smooth Muscle Cells in Valves*—The continuation of atrial subendocardial smooth muscle down into the auricularis layer of the mitral valve is illustrated in Fig 99 Figs 100–108 illustrate the occurrence of smooth muscle in mitral and aortic valves and rheumatic involvement of such smooth muscle Fig 100 shows a central avenue or track of smooth muscle that stains purple Fig 101 shows a spindle shaped lesion resembling a so-called Aschoff body, in the lower portion of the track of smooth muscle that is a continuation downward of the smooth muscle track shown in Fig 100, and Fig 102 shows in higher magnification the lesion in Fig 101 Figs 103 and 104 show smooth muscle in mitral valves and Figs 105–108 show smooth muscle in the ventricular aspect of the aortic valve The occurrence in Fig 108 of abnormal large cells in rows is like the occurrence of abnormal large cells in atrial subendocardium that MacCallum (109) described as being curiously forced into rows between elastic fibers That smooth muscle cells normally occur in atrial subendocardium in rows or strata between elastic fibers has been discussed in the immediately preceding section of this communication and illustrated in Figs 91–93 Figs 106 and 107 show that smooth muscle (stained purple) occurs in rows or strata also in the ventricular aspect of the aortic valve and the similar occurrence in Fig 108 of abnormal large cells in rows between elastic fibers in the ventricular aspect of the aortic valve strongly indicates that these large cells are smooth muscle elements and like the abnormal large cells that MacCallum (109) described as 'curiously forced into rows between elastic fibers in the atrium

C *Rheumatic Disease of Smooth Muscle Cells in Myocardial Arteries*—It has long been known as previously mentioned, that media in the arteries of the heart is often damaged in rheumatic fever (87 1?9) Vacuolation edema necrosis and fibrosis of the media which are all nonspecific changes have been described Figs 118–135 illustrate other rheumatic medial changes *some of which have to my knowledge never been described before* in rheumatic fever Figs 118–120 and 123 show multinucleated cells very probably smooth muscle cells, in the media *of arteries in the heart of patients who died* with active rheumatic heart disease Figs 121 and 122 illustrate similar multinucleated cells in the media of rabbit myocardial arteries Figs 124–126 show a *focal lesion clearly of the media,*

of a myocardial artery in which a multinucleated cell occurs and this cell is likewise very probably a smooth muscle cell Fig 127 shows in the right lower portion a defect in the *media* of a large myocardial artery Figs 128 and 129 show with higher magnification that this medial lesion comprises basophilic mono and multinucleated ragged-edged elements that are very probably derived from smooth muscle The largest cell in the upper portion of Fig 129 has at least 5 nuclei This medial lesion resembles Aschoff bodies that are derived from heart muscle cells Nodules of medial cellular elements very probably altered smooth muscle cells are seen in the lower left portion of media of an artery in Fig 130 and in the right lower portion of the media of another artery in Fig 132 and it is clear that in the case of neither of these nodular lesions is the specific character of an Aschoff body approximated On the other hand Fig 131 shows a segment of arterial media that has been converted into a lesion that comprises basophilic mono and multinucleated ragged-edged elements that are very probably of smooth muscle origin This lesion resembles an Aschoff body Finally Figs 133–135 show at different magnifications a nodular lesion that comprises slightly basophilic ragged-edged cellular elements that are very probably from medial smooth muscle elements and this lesion also resembles an Aschoff body

In connection with these findings it is noteworthy that Pappenheimer and Von Glahn (136) reported that in the media of a case of rheumatic aortitis A few multinucleated cells were seen and in another report (137) they described in rheumatic aortitis cells resembling those in Aschoff bodies in the media They did not attribute the origin of any of these cells to smooth muscle Karsner and Bayless (87) among a large number of cases of rheumatic fever in which they examined coronary arteries mentioned 4 cases in which they described extension of Aschoff bodies from outside an artery into the media of the vessel but they found no evidence that these lesions originated in the media nor did they find other lesions resembling Aschoff bodies as illustrated in the present communication that originated in the media Perry (139) published an illustration of a small nodular lesion in media of a myocardial vein in a case of rheumatic heart disease and they considered the cells in the nodule to be of non myogenic origin This nodule somewhat resembles those in Figs 130 and 132 in the present communication and did not closely approximate the specific character of an Aschoff body

VIII Reasons for the Common Misinterpretation of the Histopathogenesis and Significance of Specific Rheumatic Lesions of Muscle Cells in Rheumatic Heart Disease Special Reference to Those in Atrial Appendages

Figs 118–135 of medial lesions in myocardial arteries taken together with Figs 91–98 of atrial subendocardial smooth muscle and with Figs 99–108 of smooth muscle in rheumatic valves are evidence of focal rheumatic involvement of smooth muscle cells which can sometimes mimic Aschoff bodies To the knowledge of the writer no one has previously suggested that rheumatic disease of smooth muscle cells can result in such lesions The evidence here submitted on this point appears to be a satisfactory answer to the criticism of some (156 193) that occurrence of lesions resembling Aschoff bodies in valves and beneath the endocardium of atria constitute evidence against the myogenic origin of Aschoff bodies

The very great majority of studies to date on the pathology of rheumatic heart disease have not taken into account the occurrence and involvement of muscle cells in the following sites 1) heart muscle cells (in interstitium) between other heart muscle cells as shown in Figs 2 6 8 13 19–27 73 74 76 77 79–81 157 159 and 162 2) heart muscle cells very close to blood vessels (Figs 16 37–45 75 and 78) 3) heart muscle cells just beneath atrial and ventricular subendocardial tissue (Figs 82–90 and 160) 4) projection of myocardium into the loose sub epicardial tissue in such a way that in certain sections aggregates of muscle appear to be isolated in the sub epicardial tissue (Fig 153) 5) (striated) heart muscle cells in valves (Figs 109–116) and 6) smooth muscle cells in atrial subendocardial tissue and valves (Figs 91–108)

Utilizing the concept that Aschoff bodies develop from fibrinoid alteration of connective tissue irrespective of muscle cells Tedeschi Wagner and Pani (179) from study of 400 atrial appendages classified Aschoff bodies according to 1) early Aschoff bodies indicative of rheumatic activity and 2) senescent Aschoff bodies that are not indicative of rheumatic activity In the genesis of specific rheumatic lesions in subendocardial tissue these investigators

did not take into account primary involvement of heart muscle cells just beneath the subendocardium as illustrated previously (126) and in this communication in Figs 82–90. In their development from heart muscle cells in this site Aschoff bodies may come to lie partially in subendocardium. Furthermore, they did not consider at all the possibility of involvement of smooth muscle cells (Figs 94 and 97) in subendocardial tissue. Yet many of the "senescent" lesions that they illustrate appear to be in subendocardial tissue where smooth muscle cells occur often in abundance as here illustrated in Figs 91–98. Tedeschi, Wagner and Pani state that the nuclei of cells in "senescent" Aschoff bodies differ in appearance from those of "recent" Aschoff bodies.

The reaction of smooth muscle cells to rheumatic injury should not be expected to result in lesions morphologically identical with those of striated heart muscle cells. In my experience the specific rheumatic lesions involving smooth muscle in atrial subendocardial tissue as shown in Figs 94 and 97 do not have as large as basophilic or as "blooming" multinucleated elements as those (Figs 2, 73, 82, 159, 161 and 162) often seen in Aschoff bodies that are derived from heart muscle cells. This does not mean, however, that less rheumatic activity is denoted by lesions of smooth muscle cells or of heart muscle cells or by other rheumatic lesions with less prominent proliferative reaction of nuclei than that seen in the more florid Aschoff bodies. It is well known that in acute and relatively rapidly fatal attacks of rheumatic heart disease fresh or recent lesions of heart muscle cells and of smooth muscle cells in myocardial arteries often occur with little or no nuclear proliferation in the involved muscle cells. And it is of course widely known that in many other conditions injury to cells can result in acute degenerative or frank necrotic change in cells with little or no proliferative reaction of the involved nuclei. In the light of our evidence here presented, especially in Figs 82–98, examination of illustrations of lesions submitted by Tedeschi, Wagner and Pani that were interpreted by them as being "senescent" healed or healing lesions of connective tissue that do not indicate rheumatic activity, reveals that these are instead *active* lesions of *muscle cells*.

Furthermore with respect to the many reports of rheumatic cardiac lesions in atrial appendages it should be emphasized that nonnucleated sarcoplasmic fragments of heart muscle cells just beneath the endocardium or deeper or of smooth muscle cells in subendocardial tissue should not be misinterpreted as fragmented swollen, clumped or fused collagen, fibrinoid collagen, fibrinoid degeneration of ground substance or fibrinoid, and mono- or multinucleated sarcoplasmic fragments of smooth or striated muscle cells and multinucleated syncytial myogenic elements (Fig 160), like those in Figs 10–18 should not be misinterpreted as connective tissue cells reacting to altered connective tissue. Furthermore thick collagen laid down as scar in previous attacks of rheumatic fever or during the final one should not be misinterpreted as fresh rheumatic injury to connective tissue.

It has been suggested by Wachstein (191) that the use of a histochemical technique for succinic dehydrogenase (192) might be helpful in the identification of cellular structures derived from myocardium inasmuch as healthy heart muscle cells have been found to give a positive staining reaction for the presence of this enzyme. However, as Wachstein and Meisel have shown, disintegrating heart muscle cells in myocardial infarction fail to show this enzymatic staining reaction, and reduction of enzymatic activity was noticed by them within a few hours after the beginning of myocardial infarction in muscle fibers which showed no significant changes with routine staining techniques. By the time an Aschoff body is fully developed from damaged heart muscle cells the damaged cells have disintegrated and one would not expect the lesion to show a positive staining reaction for succinic dehydrogenase. In the light of Wachstein's investigation it would appear that the use of this technique in the study of rheumatic heart disease might be helpful in detection of the earlier changes in heart muscle cells where routine staining techniques may fail to reveal alterations of the cells. It should go without saying that failure to demonstrate succinic dehydrogenase in Aschoff bodies is no evidence whatever against the myogenic origin of these lesions.

IX VARIOUS RHEUMATIC LESIONS, OTHER THAN ASCHOFF BODIES OF HEART MUSCLE CELLS

A *Alteration of Striations and Fatty Change.* That changes in heart muscle fibers occur without proliferative or inflammatory reaction in

rheumatic heart disease has long been known (24 199) and previously referred to here Figs 137 and 138 show irregular staining of heart muscle fibers with focal interruption of their striations granular change and fragmentation in a heart that also showed many Aschoff bodies In Fig 136 is seen similar change that was widespread in the left atrial appendage of a patient with severe cardiac symptoms for several years before mitral valvulotomy No Aschoff bodies were found in this atrial appendage Figs 139–141 are from two twelve year old boys who died with active rheumatic heart disease associated with many Aschoff bodies Marked focal fatty change was widely distributed throughout the myocardium Note the myogenic nuclear elements in the track of a myofiber near the top of Fig 139 and in the track of a myofiber in Fig 142 which is from the heart of a six year old boy who died with many Aschoff bodies A strikingly similar picture of myogenic nuclear elements in the track of a myofiber can be seen in Fig 143 from rabbit skeletal muscle Fig 144 is from the heart of a thirty nine year old woman who had rheumatic fever at five years of age and progressive dyspnea associated with low grade fever in the last two years of life At the time of death she was being evaluated for mitral valvulotomy The erythrocyte sedimentation rate was very rapid several days before death At autopsy the myocardium was found to be very flabby No Aschoff bodies were found but many areas of fatty change of cardiac muscle fibers such as that seen in Fig 144 were found throughout the myocardium

B *Focal or Diffuse Necrosis of Heart Muscle Cells Associated With Inflammatory Cells and With or Without Large Cellular Elements of Myogenic Origin*—Focal infiltration of polymorphonuclear leukocytes and/or lymphocytes and plasma cells not infrequently occurs in the myocardium in rheumatic fever and atrial myocardium is a common site (180) However occasionally diffuse infiltration of the myocardium with polymorphonuclear leukocytes and/or lymphocytes plasma cells and eosinophiles occurs (6 26 57 126 150 148 161 166 205) Among the cells of the e infiltrations in some cases are interspersed cells sometimes in nodular formation characteristic of Aschoff bodies Skworzoff (166) noted that patients who showed extensive diffuse infiltration of inflammatory cells in the myocardium were usually children who experienced a stormy clinical course with rapidly fatal outcome My own findings (126) are in agreement with and extend those of Skworzoff In study of a very large number of well documented cases of active rheumatic fever extensive infiltrations with inflammatory cells mainly polymorphonuclear leukocyte were found in the atrial myocardium in association with necrosis of myofibers in several children and in the absence of atrial Aschoff bodies but in all these cases I found Aschoff bodies in the ventricular myocardium In the atrial myocardium of a ten year old boy I have seen diffuse infiltration with lymphocytes and plasma cells associated with necrosis of myofibers and cells like those characteristic of Aschoff bodies And in the atrial myocardium of a forty-one year old woman I have recently observed diffuse infiltration with eosinophiles lymphocytes and plasma cells associated with necrosis of myofibers and in the absence of atrial Aschoff bodies but many Aschoff bodie were found in the ventricular myocardium Furthermore in a fifty year old man in whom commissurotomy for mitral stenosis was recently carried out biopsied atrial appendage revealed strikingly extensive diffuse infiltration of atrial myocardium with lymphocytes and especially plasma cell associated with marked necrosis of myofiber and many multinucleated muscle cells The findings in this latter case are like those reported and illustrated by Butterfield (26) in the case of a sixteen year old girl in whom diffuse infiltrations of lymphocytic character' were found in the atrial myocardium in association with multinucleated cells like those in Aschoff bodies

In my experience focal and diffuse infiltrations of the myocardium with small inflammatory cells have invariably been associated with degeneration or necrosis of muscle cells and it appears to me that these infiltrations probably represent reaction to this marked alteration of muscle cells Figs 145–150 illustrate some of these changes Fig 145 shows focal necrosis of muscle cells associated with very slight reaction of inflammatory cells in myocardium of an atrial appendage Aschoff bodies were also found in this appendage Fig 146 shows a focal lesion in the atrial appendage of another patient This lesion comprises sarcoplasmic fragments myogenic nuclei and a rare inflammatory cell Several such lesions were found in this appendage but no

definite Aschoff bodies were found Fig 147 shows a ventricular myocardial lesion rather similar to the atrial lesion in Fig 146 The lesion in Fig 147 is in my judgment a small so-called Aschoff body As stated in the explanation of plates this figure is from a heart that contained an extraordinarily large number of lesions of heart muscle cells including very many typical Aschoff bodies several of which are seen in other figures here illustrated (Figs 2 6 20 21 23 24, 27, 50 54 55 57 60, 61 and 63) Fig 149 shows a myocardial lesion with numerous small cells associated with necrosis of myofibers in a 15 year old patient who died nine years after a recognized attack of acute rheumatic fever and about one week after onset of cough and sore throat Note the striking resemblance of this lesion to the one in Fig 148 which is from a rabbit that died with markedly irregular cardiac rhythm eight days after the last of five focal cutaneous infections with group A streptococci Scarring of these lesions would very probably result in a picture like that seen in Figs 151 and 152 that show myocardial scarring in respectively, a rabbit repeatedly infected focally with group A streptococci and a patient who died after repeated attacks of rheumatic fever Finally, Fig 150 shows a variety of changes in the left ventricle of an 8 year old girl There is seen here poor staining vacuolation and necrosis of heart muscle cells with some cellular reaction and interspersed Aschoff bodies (in the center and left uper portion of the picture)

X Specific Rheumatic Lesions of Muscle Cells Generally Referred to as Aschoff Bodies in Atrial Appendages as Unequivocal Evidence of Active Rheumatic Heart Disease

A Frequent Lack of Correlation Between Results of Clinical Laboratory Tests and The Occurrence in Atrial Appendages of Specific Rheumatic Lesions of Muscle Cells—Since patients selected for mitral commissurotomy to date have in the very large majority been considered free of rheumatic activity at the time of operation often after extensive and careful clinical examination it has appeared somewhat anomalous that specific rheumatic lesion usually referred to as Aschoff bodies, have been found in the biopsied left atrial appendage in many of these patients (from about 40% to about 65% in most series) Efforts to explain this apparent contradiction have so far been disappointing and considerable discussion has arisen concerning the significance of these lesions The occurrence of these specific rheumatic lesions in atria has not generally correlated with prolonged electrocardiographic P R intervals elevation of the antistreptolysin O titer, rapid erythrocyte sedimentation rate or the occurrence of C-reactive protein in the blood (18 47, 118 119 186) nor has the presence of these lesions appeared to be prognostic of the post-operative clinical course of these patients (46 138) These discrepancies have led some students of rheumatic heart disease to conclude that these specific atrial lesions are not indicative of rheumatic activity (48), or that the great majority of these lesions do not indicate rheumatic activity (160) although it has been found repeatedly that the occurrence of these lesions in atrial appendage correlates closely with the occurrence of Aschoff bodies in ventricular myocardium (28 41 96 102 108, 118 180)

Employing a concept that characteristic rheumatic lesions develop from a basic change in connective tissue Tedeschi Wagner and Pani (179) have interpreted rheumatic lesions in atrial appendages as being indicative of rheumatic activity only if they exhibit certain connective tissue changes and exudative inflammatory reaction If the morphological criteria and interpretation employed by the latter investigators were valid, the incidence of rheumatic activity at the time of mitral commissurotomy in a large group of patients studied by them would be only 2% (8 out of 400 patients) The criteria utilized by these investigators have been previously discussed in Section VIII of this communication and *appear to the present author* to be very arbitrary I have submitted evidence here to indicate that both 1) the lesions that they interpret as early or active lesions of connective tissue which to them indicate rheumatic activity, and 2) those that they interpret as senescent healed or healing lesions of connective tissue that to them do not indicate rheumatic activity are instead *lesions of muscle cells that signify rheumatic activity* With respect to the genesis of subendocardial Aschoff bodies in atrial appendages the latter and almost all other investigators to date have not taken into account rheumatic involvement of heart muscle cells just beneath the subendo-

cardial tissue as demonstrated in the present communication in Figs 82–90 Furthermore it appears that no one previously has taken into account rheumatic involvement of smooth muscle cells that occur often in abundance in atrial subendocardial tissue (Figs 91 98) Like smooth muscle cells in myocardial arteries (Figs 118–135) and in cardiac valves (Figs 100–108) subendocardial smooth muscle cells can react to rheumatic injury to form lesions that mimic to varying degrees Aschoff bodies that are derived from heart muscle cells

It appears that there is no laboratory test sensitive enough to detect some of the subclinical grades of rheumatic activity It seems to the writer most unwise indeed incorrect to assume as some have done (47) that if such a laboratory test as the one to detect C-reactive protein in the blood is negative even though specific rheumatic lesions such as those in Figs 82–90 and 97 are present in atrial appendages then no significant rheumatic activity is present Stollerman et al (172) reported that many patients with specific rheumatic lesions in their atrial appendage at the time of mitral commissurotomy showed no elevation in serum titer of three kinds of streptococcal antibodies and as they concluded this is evidence that the atrial lesions in such patients do not represent recent exacerbation of the disease due to antecedent streptococcal infection However it does not appear to the present author that they are justified in also concluding that the lack of significant elevation in serum titer of streptococcal antibodies is evidence that the rheumatic atrial lesions are the lingering traces of a very low grade chronic inflammation and bear little relationship to the functional state of the myocardium This point is discussed further in the next section

B *Close Correlation Between the Occurrence in Atrial Appendages of Specific Rheumatic Lesions of Muscle Cells Some of Which Resemble Closely Ventricular Aschoff Bodies and The Occurrence of Ventricular Aschoff Bodies*—Saphir (160) has recently written that the great majority of lesions in atrial appendages that have been reported by many others as specific rheumatic lesions and usually referred to as Aschoff bodies are in his judgment either not indicative of rheumatic activity or of questionable significance with respect to rheumatic activity These atrial lesions do not meet his criteria for making a definite diagnosis of rheumatic activity However autopsy findings of others (28 41 96 102 108 118 180) have clearly shown that when such atrial lesions occurred Aschoff bodies were very commonly, indeed almost always found in ventricular myocardium, moreover these latter studies have shown clearly that the absence of such atrial lesions by no means precludes the occurrence of Aschoff bodies in ventricular myocardium or of valvulitis In this connection McKeown (118) compared in 22 hearts the occurrence of specific rheumatic lesions that she referred to as Aschoff nodules in the left atrial appendage with their occurrence in the left ventricle She found these lesions in both appendage and ventricle in 17 hearts but in the remaining 5 hearts she found Aschoff nodules in the left ventricle only Thus McKeown s findings indicate that the absence of specific rheumatic lesions in atrial appendage does not preclude the occurrence of Aschoff bodies in ventricular myocardium Kuschner and Levieff (96) found that among 15 hearts with histologic evidence of rheumatic activity subendocardial Aschoff bodies were found in the left atrial appendage in 9 ventricular myocardial Aschoff bodies were found in 10 and valvulitis in 10 Thomas Averill Castleman and Bland (180) found that among 40 hearts of patients who died with active rheumatic fever Aschoff bodies were found in atrial appendage in 29 whereas Aschoff bodies were found in routine autopsy sections in 33 These authors further reported that Aschoff bodies occurred in 22 of 40 atrial appendages removed at the time of mitral commissurotomy in comparison with their occurrence in 29 of 40 atrial appendages from the patients who died with active rheumatic heart disease

Saphir s principal objection concerning the atrial lesions in question appears to be that these lesions are not identical with the true Aschoff bodies and by the true Aschoff bodies I judge he means the interstitial Aschoff bodies found characteristically in the ventricular myocardium and these lesions are derived from aggregates of heart muscle cells lying between other aggregates of muscle cells as shown in Figs 2 6 13 19–27 73 74 76 77 and 79–81 In a recent article Saphir (159) shows a lesion in atrial appendage in illustration A of

Fig 51 on page 44 which he considers to be a type of lesion that is often erroneously called an Aschoff body However, it is noteworthy that this lesion appears to be identical with the lesions that are illustrated by him as true Aschoff bodies in Fig 46 on page 36

It would appear that at least many of the *lesions in atrial appendages* that are so commonly referred to as Aschoff bodies are not morphologically identical with certain florid so called interstitial or true Aschoff bodies as Saphir calls them However I would say that if one waits to diagnose rheumatic activity until lesions are found in atrial appendage that are morphologically identical with the florid so-called interstitial Aschoff bodies that occur among bundles of myofibers deep in ventricular myocardium then rheumatic activity in atrial appendage will *rarely if ever be diagnosed* On the other hand, Figs 82–86 and 88–90 here demonstrate that lesions in atrial appendage involving heart muscle cells just beneath subendocardial tissue occur that are like and are just as specifically rheumatic as lesions involving ventricular heart muscle cells just beneath the subendocardial tissue (Fig 87) And yet these specific subendocardial lesions of atrial and ventricular myocardium may not be morphologically identical with larger lesions that involve a greater number of muscle cells among bundles of myofibers deep in ventricular myocardium

C *Importance of Recognizing The Myogenic Nature of Specific Rheumatic Lesions in Atrial Appendage and Ventricular Myocardium to The Understanding of The Pathologic Physiology and Failure of The Heart in Rheumatic Heart Disease*—Some investigators (179) have insisted that it is imperative to comprehend that the characteristic and specific rheumatic cardiac lesions develop from primary and essential alterations of connective tissue quite irrespective of muscle cells before one can properly interpret whether or not changes in atrial appendages are indicative of rheumatic activity I reply that the evidence here submitted demonstrates that the concept that so-called Aschoff bodies are non myogenic lesions that are derived from primary and essential alteration of connective tissue is not valid Furthermore the evidence submitted here and previously (126) demonstrates that specific rheumatic lesions found in subendocardial tissue or subjacent myocardium in atrial appendages represent reaction of smooth muscle cells or striated heart muscle cells to rheumatic injury (Figs 82–98) and studies at autopsy by *others (28 41 96 102 108, 118 180)* have shown that when such rheumatic lesions are found in atrial appendage then so-called Aschoff bodies are at least very likely to be present in ventricular myocardium Furthermore evidence presented here and previously (123 126) shows that the so-called Aschoff bodies in ventricular *myocardium are derived from heart muscle cells* The conclusions appear to be well justified therefore that occurrence of these specific rheumatic lesions in atrial appendages 1) is in itself evidence of active rheumatic disease of muscle cells in atria and 2) signifies great likelihood of active rheumatic disease of heart muscle cells in ventricular myocardium even though no *electrocardiographic evidence of rheumatic activity* may be found C-reactive protein may not be present in the blood the erythrocyte sedimentation rate may be normal and there may be no serological evidence of a recent infection with group A streptococci Furthermore it is clear that the absence of specific atrial lesions does not preclude significant rheumatic activity involving heart muscle cells in ventricular myocardium

Those who fail to recognize that the lesions here discussed signify rheumatic disease of muscle cells in the heart will be at a disadvantage in efforts to explain the natural history of rheumatic heart disease and to understand the pathologic physiology and failure of the myocardium in this disease

XI The Importance of Active Rheumatic Disease of Heart Muscle Cells to Cardiac Failure

A *The Relation of Active Rheumatic Disease of The Myocardium to Cardiac Failure in Children and Young Adults Often Without Appreciable Valvular Deformity The Systolic and Diastolic Murmurs Caused By Active Rheumatic Disease of The Myocardium With Cardiac Dilatation*—Abundant evidence indicates that in children with rheumatic heart disease cardiac failure very often associated with considerable cardiac dilatation is primarily if not essentially the result of active rheumatic disease of the myocardium (20 36 51 104 105 155 199 204) and the cardiac failure in children is often not associated with valvular deformity Lees and

Poynton (105) in 1897–98 demonstrated the frequency of cardiac dilation in children *and young* adults with acute rheumatic fever and/or chorea They noted that even though dilatation was frequently marked the clinical symptoms of *the patients at rest* were remarkably slight In fatal cases they confirmed at autopsy their clinical finding of cardiac dilatation very often in the absence of valvular deformity and excess pericardial fluid Poynton and later Coombs (39) considered rheumatic disease of the myocardium to be of great *importance to* cardiac failure not only in children but in adults as well even though the morphological change that they observed in the myocardium was slight

West (199) in *1878* and Coombs (36) in 1924 emphasized the *causative relation of* cardiac dilatation to systolic and even diastolic murmurs in attacks of rheumatic fever Bland Jones and White (20) in 1936 reported on the disappearance of apical systolic and diastolic murmurs in 83 rheumatic *patients from 8 to 18* years of age who were initially considered to have active rheumatic valvular disease on the basis of the occurrence of the systolic and diastolic *murmurs In 53 of the 83* patients mitral stenosis and regurgitation *were diagnosed at the* time of the initial examination However neither a systolic nor a diastolic murmur could be heard even after exercise of the patients and other effort *to detect them* in any of the *53* patients 3 to 5 years later They *stated the following*

In those patients who were considered to have mitral valve involvement on the basis of apical *systolic* and diastolic murmurs the diastolic murmur was invariably *the* first to disappear Occasionally this apical diastolic *rumble subsided* within a few months after the onset of rheumatic infection during the period while the patient *was convalescing* and still under observation in the hospital In these cases they attributed the apical systolic and diastolic murmurs that *were* initially heard to cardiac dilatation related to rheumatic activity Usually they noted more *gradual regression of* the murmurs over a period of years F M Smith in discussion of this paper stated his opinion that subsidence of active rheumatic disease of the myocardium was for the *most part* responsible for the disappearance of the murmurs in all 83 *cases Bland* et al also reported that in many other patients they noted marked regression of murmurs These investigators and Bohan in discussion of their paper referred to adult cases in which mitral stenosis *had been* diagnosed in life but was not found at autopsy

Wilson and Lim (204) have emphasized the relation of cardiac dilatation to diastolic and systolic murmurs that appeared in children during attacks of rheumatic fever and regressed with *improvement of the patients With the latter* investigators I have observed *in the case of a* 3 year old child who developed a definite apical diastolic murmur and showed at autopsy a mitral valve of normal thickness except for a *row of tiny verrucae the following* extensive disease of the heart muscle *cells including* very many Aschoff bodies and many foci of non specific necrosis of muscle cells some of which were associated with considerable infiltration of *inflammatory cells* And in a *14* months old child who died *after developing an* apical diastolic murmur and showed at autopsy *mitral* leaflets only slightly thickened I have observed very extensive disease of heart muscle cells including many Aschoff bodies and focal necrosis of heart muscle *cells in many areas* associated with small inflammatory cells

In some patients on the other hand as Coombs (39) stated when a murmur previously heard clearly becomes less audible and disappears *altogether it is often* a sign of increasing muscular failure For instance *when* the mitral systolic murmur heard in the carditis of childhood becomes less distinct during an *acute bout it* is a sign of decreasing muscular power In this *connection it is* pertinent to mention that I have several times detected *the* disappearance a few weeks or several days before death of systolic murmurs that had developed in *rabbits after repeated* focal infections with group A streptococci and *at autopsy the* prominent findings in these animals were in the myocardium

In 1934 Rothschild Kugel and Gross (155) reported results *of a clinical* pathological study on the incidence and significance among 3000 patients who were autopsied of active rheumatic disease of the heart in cases which presented *anatomically* and histologically unmistakable evidence of present or *past rheumatic* heart disease and in which complete anatomical investigation had been made These rheumatic cases numbered 161 and ranged from 17 months to 80 years of age *There* were 22 cases between 1 and 10 years of age All of these *patients* succumbed

to myocardial failure The authors found that 'In all the e ca es the degree of the mechanical defect was so slight that it obviously bore no relationship to the myocardial failure' A choff bodies were found in 20 of the e 22 cases There were 44 cases between 10 and 20 years of age and in 41 of these there was active rheumatic myocardial disea e In 35 of these 41 ca es in which the patients died of myocardial failure and in which the degree of the valvular defect was tudied 9 showed a tight mitral stenosis and 2 moderate valvular stenosis Among the 41 patients with active rheumatic disea e of the myocardium A choff bodies were found in 37

B *Cardiac Failure in Patients With Mitral Stenosis Special Reference to The Considerable Benefit From Mitral Commissurotomy in Many Cases, and Lack of Correlation in Many Cases Between Subjective Improvement and Objective Clinical Findings After Operation*—Poynton Coombs and Rothschild Kugel, and Gross and others considered active rheumatic disea e of the myocardium to be of great importance to cardiac failure not only in children but al o in adults with or without valvular deformity However they and A choff and the great majority of pathologists have not recognized the involvement of heart muscle cells in the so-called Aschoff bodies and other myocardial lesions in patients with rheumatic heart di ease This widespread lack of recognition of the myogenic nature of these lesions and the long held and widespread assumption that they are non myogenic lesions of connective tissue gave ri e to the quandary recently expres ed by Pinninger (140) as follows Until the relation between the abnormalities in the connective tissue and myocardial failure is understood the significance of the e histological changes will remain obscure And Kuschner and Levieff (96) recently stated As Pinninger *has pointed out, we do not as yet understand* how the Aschoff body a lesion of the interstitial connective tissue affects myocardial function

It appears to be well recognized that active rheumatic disea e of the myocardium is of primary importance to heart failure in children (even though involvement of the heart mu cle cells themselves as here demon trated is still very generally *not recognized*) In explanation of cardiac failure in rheumatic heart di ease in adults on the other hand especially in patients with mitral stenosis there has been an increasing tendency in recent years to minimize and even disregard the role of rheumatic lesions of the myocardium, especially those that represent active di ease (54) In 1954, Wilson and Greenwood (203) stated There is considerable doubt about the functional importance of lesions in the myocardium een in adult rheumatic heart disease"

In the light of the widespread lack of understanding of the involvement of heart muscle cells in the so-called A choff bodies and other myocardial lesions as here demonstated, it is perhaps understandable why there i such considerable and widespread doubt about the functional importance of rheumatic lesions in the myocardium in rheumatic heart di ea e in adults But I would emphasize the following If active rheumatic di ease of heart mu cle cells can cau e failure of children s hearts without the burden of valvular deformity and even without valvular *thickening then it is* likely that active rheumatic di ease of heart mu cle cells can cause failure of adult hearts especially those burdened with valvular deformity and with myocardium damaged by previous attacks

The results of commissurotomy for mitral stenosis have hown that this operation is of considerable benefit to properly selected patients (10 11 46 62 173) Indeed very striking improvement in certain patients has been reported by *many observers It appears that the most* suitable candidates for this operation are tho e patients with tight mitral stenosis with a minimal degree of insufficiency who have shown disabling symptoms of cardio pulmonary dysfunction for a fairly short period of time (46 61 62 173) The more marked the degree of associated mitral insufficiency and the more advanced the state of congestive failure the less likelihood there is of benefit from the operation (46 173) Ellis Harken and Black (46) have recently reported moderate to marked improvement following commissurotomy even in 55% of 206 patients who were mostly cardiac invalids suffering from chronic congestive failure or who were maintained in a precarious state of compensation only by vigorous medical means

Some ob ervers have found that the subjective improvement in many patients after mitral commi surotomy was not associated with improvement in objective clinical findings in par

ticular cardiac murmurs heart size and elec trocardiographic findings (15 45 169) In 20 patients followed in serial roentgenological study for periods varying from 6 months to 2 years Soloff and Zatuchni (169) found that the number of patients with increase in heart size after commissurotomy was greater than the num ber of patients that showed no change or decrease in heart size and they attributed the increase in heart size to intensification or reactiva tion of rheumatic carditis Bergy and Bruce (15) found on post-operative evaluation of 31 pa tients at an average of 21 months after mitral commissurotomy that there was considerable discrepancy between subjective improvement on the one hand and objective findings in re sponse to standard exercise tests on the other In a roentgenological study carried out for from 12–30 months (average about 19 months) after mitral commissurotomy in 55 patients Gary (56) found that even though 44 of the 55 pa tients were able to resume normal or almost normal activity the majority showed no de crease in heart size and in some the heart had become definitely larger In some patients de layed post-operative improvement and prolonged convalescence has occurred and in others post operative improvement has been followed in several months to a few years by deterioration of cardiac status (12 25 46) Pampush and Bruce (134) studied the clinical course and tolerance of standardized exercises of 15 pa tients with mitral stenosis who did not undergo surgical treatment of the mitral valve for a variety of reasons When the patients were re evaluated one year later it was discovered that the three patients with poorest functional capac ity (class IV N Y Heart Association classifi cation) had died despite the fact that their ages ranged from 35–40 years In the 12 surviving patients with class I II or III functional capac ity reduction had occurred in incidence of symptoms and signs as well as treatment of pulmonary and cardiac edema Harvey et al (73) emphasized the importance of recognizing those rheumatic patients with mitral stenosis in whom myocardial insufficiency was primarily important They stated that in such patients in the absence of moderate to severe degree of pulmonary hypertension at rest probably little or no important degree of mitral block exists Such patients numbered 8 among 45 patients with mitral stenosis who were studied physiologically by them as possible candidates for mitral commissurotomy Ellis et al (46) recently stated that Myocardial failure is undoubtedly an important element in the poor results of some of the patients or in the deterioration of others and Baker and Hancock (12) consider that a myocardial factor may contribute to the deterioration and may well be present in those who still maintain good results

C *Lack of Correlation Between The Degree of Mitral Stenosis and Cardiac Disability and Between The Degree of Mitral Stenosis and Pulmonary Vascular Change Special Reference to Unoperated Patients With Marked Mitral Stenosis With Little or No Signs of Congestive Heart Failure Even at Advanced Age*—It has long been known that in cases of rheumatic heart disease with mitral stenosis the degree of mechanical obstruction due to the stenosis does not necessarily correlate with either the occur rence extent or time of onset of cardiac failure Some patients with considerable even very marked mitral stenosis can live well past the age of 70 sometimes with little or no evidence of cardiac failure Rothschild Kugel and Gross (155) in report of a clinical pathological study of 161 patients who died with evidence of rheumatic heart disease either active or inactive commented that it was striking to note the high grade of mechanical defect existing in individ uals living to the 5th and 6th decade with little or no evidence of congestive failure They also reported on two patients with moderate mitral stenosis who survived to the 8th decade Another patient a woman of 80 years with tight mitral stenosis and marked aortic stenosis died of thrombosis of a mesenteric artery with no signs of cardiac failure White and Bland (201) reported on 4 patients with moderate mitral stenosis who lived beyond 80 years of age and on one patient who died at 73 years of age of bronchopneumonia with but little heart failure associated with extreme fish mouth mitral stenosis

Graham et al (65) reported on correlation of post mortem findings with the clinical course in 101 cases of mitral stenosis In a considerable proportion of these patients especially of those over 50 years of age rheumatic heart disease was either not diagnosed during life or only during the terminal illness Severe mitral stenosis was not uncommon in the older age group in

deed 21 of the 58 patients over 50 years of age and 16 of the 38 patients over 60 years of age had mitral stenosis of the most severe grade (Grade III) Although of the 101 patients studied 47 had very marked stenosis of fish mouth severity the clinical records indicated that 15 of these 47 patients had little or no cardiac disability up to the time of their death or until the terminal part of their illness 16 of the patients with extremely stenotic mitral valves lived over 60 years and 3 patients lived over 70 years These findings show that mitral stenosis of a severe grade may be tolerated by some patients for a protracted period with either little or no impairment of cardiac reserve This was also apparent in their analysis of patients in whom rheumatic heart disease was not diagnosed during life There were 31 in this group and 6 of them had marked mitral stenosis All 6 of these and 21 of the total of 31 were able to carry on with either no cardiac symptoms or with mild dyspnea only prior to their terminal illness They further reported that of 45 patients with the most severe degree of mitral stenosis 12 had no demonstrable organic changes in the pulmonary circulation and in 17 the changes were only mild and in only 6 of the 45 were pulmonary changes reported as marked In a companion study Ellis et al (44) reported on 10 patients with very marked fish mouth mitral stenosis and 2 patients with stenotic mitral valve admitting one finger who died after physiologic measurement (particularly of the cardiac output and pulmonary vascular pressure) had been correlated with the clinical states of the patients They stated It was found that the degree of mitral stenosis and the degree of pulmonary vascular change could not be closely or accurately correlated either with the degree of disability of the patient or with decrease of cardiac output or increase in pulmonary pressure although of course there was a general tendency for such correlations to exist Active rheumatic myocarditis was found at post mortem examination to be present in several patients in whom it was not clinically diagnosed

D *The Relation of Active Rheumatic Disease of The Myocardium to Cardiac Failure in Patients of The Third, Fourth and Fifth Decades of Life and Older*—Krehl (94) in 1889 from careful clinical pathological study of 10 patients chiefly elderly people with valvular deformity concluded that progressive changes in the myocardium are more important to heart failure than the valvular defects He emphasized the great variability with which the hearts of patients with similar degree of valvular deformity tolerated burdens such as walking various distances stair-climbing weight lifting or some superimposed non rheumatic disease With the microscope he observed various cellular and degenerative changes in the myocardium in addition to sclerotic changes in coronary arteries and arterioles in these patients Rothschild, Kugel and Gross (155) carried out a clinical pathological study of 161 patients who died with rheumatic heart disease either active or inactive for the purpose of correlating the occurrence of myocardial failure the degree of valvular defects and the presence of myocardial disease together with the various age periods in which death occurred They concluded While the causal relation of active myocarditis to circulatory failure is very striking in the first 2 decades of life it is not sufficiently appreciated that in cases of rheumatic heart disease in adults of the the 3rd 4th and 5th decades of life a recurrent rheumatic myocarditis rather than healed mechanical defects may in the majority of instances be the precipitating cause of the circulatory failure They emphasized that individuals with quiescent rheumatic heart disease and considerable valvular deformity may reach the 7th and 8th decades of life and die of a totally unrelated disease without having had any evidence of cardiac failure directly attributable to their valvular deformity

Werner (198) from study of 100 consecutive cases of cardiac failure in patients with rheumatic heart disease (ranging in age from 5 to 69 years median age 31) concluded that it is not only infection but a specific rheumatic infection that is the important factor in the production of heart failure Juster (86) carried out a clinical study of 59 ambulatory cases of chronic rheumatic heart disease in women between 15 and 44 years of age who were followed for a period of 1–29 months (average of 13 7 months) In the course of this study regular sinus rhythm gave way to atrial fibrillation in 9 cases and it appeared to Juster that in each instance the cardiac irregularity supervened during periods of rheumatic activity On the other hand it appeared to him that in certain

ca_es rheumatic activity was compatible with normal cardiac reserve He concluded that in many adult ca es prolonged and progressive ac tive rheumatic heart disea e per ists sometimes so mild as to be scarcely detectable but some times exhibiting high grades of severity

Even in rheumatic patients in the 6th and 7th decades of life active rheumatic disea_e of the myocardium occurs in as ociation with cardiac decompensation A_choff bodies in the myocar dium have been repeatedly found in patients in this age group (50 67 113 126 145 152) In such patients active rheumatic disea_e of the myocardium is usually not suspected clinically instead the cardiac decompen_ation is usually attributed entirely to valvular deformity Ferris and Myers (50) reported on 3 patients between 61 and 79 years of age who died with numerous myocardial A choff bodies and only light val vular changes In a 59 year old woman who died suddenly and without a diagnosis of rheu matic activity Mallory (113) found on micro- scopic examination that The heart shows more A_choff bodies per cu mm than any heart I have ever seen In this case there was mild mitral stenosis with calcified leaflets but no great shortening of chordae In a case of rheu matic heart di ease in a 61 year old woman Rakov and Taylor (145) reported that Histo logic studies revealed the large t and greatest number of A_choff bodies in the myocardium that we have ever seen There was moderate thickening of the mitral valve and some chordae Rogers and Robbins (152) reported the occur rence of Aschoff bodies in several patients over 60 years of age in whom rheumatic activity had not been diagno ed and they emphasized the importance of the active myocardial di ease to cardiac failure in these patients I have recently ob erved a case in which very extensive active rheumatic disea_e of heart mu_cle cells including a very large number of Aschoff bodies occurred in association with cardiac failure in a 60 year old woman with moderate mitral stenosis and rheumatic activity was not diagno ed before death

In the light of the foregoing evidence of evere active rheumatic myocardial disease a ociated with cardiac failure in adults it is surpri ing to note a recently expre__ed view (54) that con gestive heart failure in adults with rheumatic heart disea_e should rarely if ever be attributed to activation of rheumatic fever The lack of correlation reported to date between the occur rence of specific rheumatic lesions generally referred to as Aschoff bodies in atrial append ages and the pre- and postoperative course of patients who have undergone mitral commis surotomy has been pointed to by some as a reason for believing that these lesions are not indicative of active rheumatic disease and also as evidence that rheumatic activity is not im portant to cardiac failure in the e patients This view has recently been expressed by Friedberg (54) as follows The development or progres sion of heart failure in the adult with rheumatic heart di_ea e is often attributed to active rheu matic fever especially if the patient is febrile These diagnostic concepts are based on the traditional teaching that rheumatic fever is a per istent chronic di ea e with a tendency to recrude cence throughout life This teaching in turn was based on po t mortem findings of As choff bodies in the myocardium of patients in the third to ixth decades who died of rheu matic heart di ea_e and heart failure long after the overt acute attacks of rheumatic fever The Aschoff body was interpreted to signify active rheumatic fever This interpretation and the concepts based on it are no longer tenable ince biopsy pecimens of left atrial appendages have disclosed a high incidence of Aschoff bodies without relation to the clinical picture and sub sequent course leading to the conclusion that the pre ence of Aschoff bodies cannot be re garded as evidence of clinically active rheumatic fever If further studies support evidence that there are fresh and senescent A_choff bodies that can be differentiated by special stains the fresh A choff body may be found to be accept able as a pathological criterion of clinically ac tive rheumatic fever

In reply to the views quoted in the above paragraph I will first refer to the evidence sub- mitted here in Figs 82–98 and 160 and dis cus_ed in ections VI G VII VIII and X of this communication and al_o to evidence previ ou ly submitted (126) which shows that pecific rheumatic le ions generally called Aschoff bodies in atrial appendages represent active rheumatic le ions of two kinds 1) A_choff bodies that originate from rheumatic damage to (striated) *heart muscle cells* usually just be neath the subendocardium (Figs 82–86 and 88–90) and 2) lesions that originate from rheumatic damage to *smooth* mu cle cells in subendo-

cardial tissue (Figs 94–97) and sometimes closely resemble Aschoff bodies that are derived from heart muscle cells This evidence indicates that the classification or division by Tedeschi, Wagner and Pam (179) of Aschoff bodies into fresh and senescent forms on the basis of changes in connective tissue irrespective of muscle cells is not only arbitrary but it is incorrect Most unfortunately this classification draws attention away from the most important changes in the atrial appendages, namely those of muscle cells that signify that active rheumatic disease of muscle cells is also very probably present in the ventricles

Friedberg states that the high incidence of Aschoff bodies in atrial appendages is without relation to the clinical picture However, a large proportion of if not most patients who submit to mitral commissurotomy do so because of progressively worsening symptoms of congestive failure Friedberg further writes The modified Jones criteria quite properly list congestive heart failure as a criterion of rheumatic carditis only in patients below the age of twenty five Beyond that age heart failure is most probably due to other causes that cannot be excluded But it would appear to be very arbitrary to limit the use of congestive heart failure as a criterion of active rheumatic heart disease to the first 2½ decades of life The finding of Aschoff bodies in patients with rheumatic heart disease who die in the 4th and 5th decades because of myocardial failure has been previously here referred to (155) Evidence even in patients in the 6th 7th and 8th decades of congestive heart failure leading to death and due to active rheumatic myocardial disease that was undiagnosed before death has also been here cited

In discussion of rheumatic heart disease in adults Coombs (39) stated the following Symptoms are more important than signs and when it comes to signs those that indicate the condition of the muscle are of more value than those arising directly from the valvular changes It has been shown by many other observers that there is a close correlation between the occurrence of the specific rheumatic lesions in atrial appendages as illustrated in Figs 82–86 88–90 94 96 and 97 and generally referred to as Aschoff bodies and occurrence of typical Aschoff bodies in ventricular myocardium (28 41, 96, 102, 108 118 180) It has also been shown that the absence of these specific atrial lesions does not preclude the occurrence of ventricular Aschoff bodies (118, 180)

Thus the occurrence of these specific atrial lesions is in itself evidence of active rheumatic disease of muscle cells in the heart, even though there may have been no recent progression of symptoms of congestive failure prior to commissurotomy, no electrocardiographic evidence of rheumatic activity may be found, C-reactive protein may not be present in the blood, the erythrocyte sedimentation rate may be normal and there may be no serological evidence of a recent infection with group A streptococci

E *The Relation of Specific Rheumatic Lesions of Muscle Cells Generally Called Aschoff Bodies in Biopsied Cardiac Atrial Appendages to The Pre Operative Clinical Course of Patients Between 20 and 40 Years of Age With Signs of Mitral Stenosis Who Underwent Cardiac Surgery* —With respect to the widely held assumption that the occurrence of specific rheumatic atrial lesions bears no relation to the clinical course of patients undergoing mitral commissurotomy I will refer to the work that has been recently carried out and is being continued by Dr Frederic G Dalldorf and me (40) on the relation of specific rheumatic lesions generally called Aschoff bodies in cardiac atrial appendages to the preoperative clinical course of patients with rheumatic heart disease who underwent mitral commissurotomy

Many if not most patients who submit to mitral commissurotomy do so because their symptoms of cardiac disease are *progressively* worsening This raises the question Why does the cardiac status of these patients deteriorate? It occurred to us that in these patients active rheumatic myocardial disease is an important factor as it is in younger adults and children and this is indicated by the frequent occurrence of specific rheumatic lesions of muscle cells (Figs 82–86 88–90 97 and 160) generally called Aschoff bodies, in surgically removed atrial appendages If this were true then in a group of patients free of other cardiovascular diseases and conditions which might contribute to failure of an already damaged heart a definite correlation might be discovered between the preoperative clinical course and findings in atrial appendage

Only patients below the age of 41 years were selected for this study to minimize the effect

of nonrheumatic arteriosclerotic cardiovascular disease. We obtained the clinical histories of all patients under the age of 41 years who underwent mitral commissurotomy before 1957 in the department of surgery of the New York Hospital. Histories in these cases had been recorded in detail by at least three observers on each admission. Two patients were excluded because their histories were inadequate and 15 cases were eliminated because of the following conditions: 11 patients were pregnant at the time of operation, 1 patient had experienced repeated episodes of pulmonary embolization, 1 patient was hypertensive, 1 patient had diabetes mellitus and 1 patient was considered to have Lutembacher's syndrome. In examining the clinical histories particular attention was paid to the time of onset and to progression of cardiac symptoms prior to operation. Emphasis was placed on such symptoms as increasing exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, episodes of hemoptysis and worsening fatigue. The patients were classified into three major groups. Group I consisted of those patients who showed steadily progressive worsening of cardiac symptoms with evidence of progressively decreasing cardiac reserve for *18 months or less* prior to operation (35 patients); 11 of these had been entirely asymptomatic before their preoperative deterioration. Group II comprised those patients who had shown steadily progressive worsening of their cardiac symptoms and evidence of progressively decreasing cardiac reserve for a period *longer than 18 months* prior to operation (33 patients). Group III comprised those patients who likewise had severe rheumatic heart disease but had shown no evident deterioration of their cardiac status during the two years prior to operation (13 patients). The 68 patients showing deterioration prior to operation, *i.e.* those in *Groups I and II*, were further subdivided into subgroups a and b depending upon the degree of worsening. Those who had experienced well documented *marked* deterioration were classified in subgroups a while those whose deterioration was less marked and sometimes difficult to be sure of were classified in subgroups b. These subdivisions brought the total number of clinical groups to five (Ia, Ib, IIa, IIb and III). Examination of the clinical records and decisions as to clinical grouping were made without knowledge of findings in the atrial appendage.

The original sections stained with hematoxylin and eosin of the atrial appendages as well as 3 new sections in each case cut from the paraffin blocks and stained respectively with hematoxylin and eosin, phosphotungstic acid hematoxylin and Masson trichrome were examined. The amount of atrial tissue was inadequate in 5 cases and they were excluded. The histologic material was classified simply as those cases with and those without specific rheumatic lesions of muscle cells (generally referred to as Aschoff bodies).

The final sample consisted of the clinical histories and atrial tissue from 81 patients, 64 women and 17 men, ranging in age from 20 to 40 years.

As seen in Table I, the specific rheumatic lesions were found in 38.5% of patients with severe rheumatic heart disease in whom no evident deterioration of cardiac status occurred in the last two years prior to operation (Group III). On the other hand these lesions were found in 76.5% of patients showing marked progressive worsening of cardiac symptoms for longer than 18 months prior to operation (Group IIa). These lesions were found in 86.5% of all patients showing marked progressive worsening of cardiac symptoms prior to operation (Group Ia and IIa combined). And finally it can be seen that these lesions were found in 95% of those patients with marked progressive worsening that began only 18 months or less prior to operation (Group Ia). The only patient of this last group in whom Aschoff bodies were not found showed numerous small foci of necrosis of heart muscle cells.

It appears evident that a significant relationship has been demonstrated in this study between the pre-operative clinical course of patients with rheumatic heart disease who underwent mitral commissurotomy and the occurrence of specific rheumatic lesions in surgically removed left atrial appendage.

It is probable that rheumatic heart disease is sometimes a chronic smoldering pathologic condition with episodes of remission and exacerbation. Much evidence indicates that many episodes of rheumatic activity do not produce the clinical manifestations classically considered to be characteristic of an attack of rheumatic fever. And many of these episodes must be clinically mute in view of the large number of patients severely handicapped with rheumatic

TABLE I†

Occurrence of Specific Rheumatic Lesions in Atrial Appendages in Relation to Duration and Severity of Preoperative Deterioration of Cardiac Status in 81 Patients Between 20 and 40 Years of Age*

Clinical group based on progression of symptoms prior to commissurotomy			Specific Rheumatic Lesions		Age of patients in groups		Normal Sinus Rhythm
Group	Duration of progression	Severity of progression	Number with lesion / Number in group	(Percent)	Average	Median	(Percent)
Ia	18 months or less	Marked definite	19/20	95 0	30 9	31	90 0
Ib	18 months or less	Minimal indefinite	10/15	66 7	34 4	36	46 6
IIa	Longer than 18 months	Marked definite	13/17	76 5	32 0	32	70 6
IIb	Longer than 18 months	Minimal indefinite	5/16	31 3	34 4	35	43 7
III	No progression of symptoms for at least two years		5/13	38 5	31 7	31	38 5
Total			51/81	63 0			

* The term specific rheumatic lesions in atrial appendages is used in reference to 1) Aschoff bodies that originate from rheumatic damage to (striated) *heart muscle* cells usually just beneath the subendocardium (Figs 82–86 88–90) and 2) lesions generally designated Aschoff bodies by others that originate from rheumatic damage to *smooth muscle* cells in subendocardial tissue (Figs 94–97) and sometimes closely resemble Aschoff bodies that are derived from (striated) heart muscle cells

Statistical analysis (168) of the incidence of specific rheumatic lesions in atrial appendages in the various clinical groups

Groups Ia + IIa compared with Groups Ib, IIb, III $\chi^2_{(1)}$ = 12 8 0 001 > p > 0 0001
Groups Ia + IIa compared with Group III $\chi^2_{(1)}$ = 9 0 0 01 > p > 0 001
Groups Ia + Ib compared with Group III $\chi^2_{(1)}$ = 6 98 0 01 > p > 0 001
Group Ia compared with Group III $\chi^2_{(1)}$ = 10 3 0 01 > p > 0 001

† This table is essentially like Table I in the paper by Dalldorf F G and Murphy G E entitled *Relationship of Aschoff Bodies in Cardiac Atrial Appendages to the Natural History of Rheumatic Heart Disease* in press in Am Jour Path vol 37 Nov 1960 Permission has been granted by the editor of that journal to reproduce this data here

heart disease who give no history of experiencing an attack of rheumatic fever or chorea This is further borne out by our finding of specific histologic evidence of active rheumatic heart disease as manifested by rheumatic lesions of atrial muscle cells in 38.5% of those patients (Group III) with severe rheumatic heart disease who showed no evident deterioration in their cardiac status in the last two years prior to commissurotomy However, other findings shown in Table I indicate that when sub-clinical episodes of rheumatic activity occur in patients with hearts already severely damaged by previous rheumatic disease they often manifest themselves by progressive worsening of cardiovascular symptoms (Groups I and II) Indeed it appears to us that the chief cause of cardiac decompensation in patients with rheumatic heart disease at least through the age group here studied is rheumatic activity itself

Strong evidence shows as discussed in section X that the presence of the specific rheumatic lesions of muscle cells that are generally called Aschoff bodies in atrial appendage is diagnostic of active rheumatic heart disease As previously mentioned in section X.B combined biopsy autopsy findings of others (28 41 96 102 108 118 180) have clearly shown that when these atrial lesions were found at the time of mitral commissurotomy typical Aschoff bodies were nearly always found in ventricular myocardium and moreover, it has been shown

that the absence of such atrial lesions does not preclude the occurrence of ventricular Aschoff bodies (118 180) However the presence of the atrial lesions in itself is not prognostic of the *post operative* clinical course or of future events in the natural history of a patient's rheumatic disease If a patient has active rheumatic disease of given intensity on the day of commissurotomy it does not necessarily follow that this particular episode of activity will long continue at the same intensity and lead to recurrent decompensation associated with progressive myocardial changes and/or new valvular alterations Indeed the surgeon may fracture the patient's mitral valve near the end of a phase of rheumatic activity and in such instances one would observe marked post operative improvement due not only to improved hemodynamics related to commissurotomy but also to improved function of the myocardium resulting from remission of activity By the same token absence of rheumatic activity at the time of operation does not preclude reactivation of rheumatic activity at a later date associated with worsening of myocardial status Although the question has not been answered satisfactorily it is possible that transient reactivation of rheumatic activity or intensification of existing sub clinical rheumatic activity results from cardiac surgery in some patients On the other hand however it is likely as Black and Harken (19) have stated that in some patients although rheumatic activity is present the patient with significant valvular obstruction may handle that myocardial disease better after the obstructing factor has been relieved

One may inquire Why does the incidence of active rheumatic lesions among biopsied atrial appendages of patients undergoing mitral commissurotomy appear to be significantly higher than the reported incidence of Aschoff bodies among hearts in most series of autopsied patients with rheumatic heart disease (31 70 96)? This should not be surprising when one realizes that in comparison with biopsy series autopsy series of cases of rheumatic heart disease usually include older patients many of whom died after rheumatic disease had become quiescent Furthermore many of these people although they showed marked stigmata of rheumatic heart disease died because of an unrelated disease as shown in the study of Rothschild Kugel and Gross (155) My own experience has taught me that in examination of the heart of patients with rheumatic heart disease who die and show no histologic evidence in a single routine section of myocardium one should always bear in mind as Gross and Ehrlich (70) emphasized that the number of blocks of the heart that are studied and the sites from which the blocks are taken will have an important bearing on whether or not so called Aschoff bodies are found Gross and Ehrlich found these lesions in approximately 59 6% of 161 patients ranging in age from 17 months to 80 years who presented anatomically and histologically unmistakable evidence of present or past rheumatic heart disease Among 46 patients ranging in age from 20 to 40 years they found Aschoff bodies in 67 4% In comparison it is noteworthy that in the recent study by Dalldorf and myself specific rheumatic lesions (generally called Aschoff bodies) of 1) heart muscle cells or 2) subendocardial smooth muscle cells were found in the left atrial appendage surgically removed at the time of mitral commissurotomy in 63% of 81 patients ranging in age from 20 to 40 years

In 1924 Coombs (39) after many years of intensive clinical pathological study of rheumatic heart disease made the following statement The more I see of the microscopic and macroscopic appearance of the rheumatic heart the more am I convinced that even in the most chronic and apparently extinct lesions it is wrong to forget the possibility of active infection

XII Lesions of Blood Vessels in The Heart and Their Relation to Myocardial Damage

Any thorough explanation of myocardial damage in rheumatic fever must take into consideration the fact that coronary arteries and their branches are frequently damaged in this disease The occurrence of arterial lesions in rheumatic fever has been recognized for over 80 years (94 129 144) and extensive description and review of rheumatic vascular lesions may be found elsewhere (71 87 93 137 153) Krehl (94) Romberg (153) Fahr (49) Swift (174) and Karsner and Bayless (87) considered lesions of myocardial arteries important to myocardial damage in rheumatic fever All coats of coronary arteries and their branches including arterioles may be involved and capillaries may be prominently involved Marked hyperplastic intimal

rheumatic changes may cause significant narrowing of arterial lumina, especially of small and medium sized vessels In some arteries medial degenerative and/or hyperplastic changes are prominent Fragmentation of the internal elastica of arteries is often found Gross, Kugel, and Epstein (71) described several characteristic rheumatic lesions of coronary arteries One of the most characteristic of these results in intimal musculo elastic hyperplastic change that in medium sized and small myocardial arteries may cause significant luminal narrowing and sometimes appreciable narrowing of large coronary arteries occurs Although proved thrombosis of large coronary arteries is rare in rheumatic fever this is not true of cardiac pain, including that of angina pectoris Gross and associates (71) described occluding platelet thrombi in the left circumflex coronary artery and major branches associated with extensive myocardial infarction in a fatal case of rheumatic fever in a 17 month old child Thrombosis of small myocardial arteries and arterioles has been repeatedly found in rheumatic fever (39, 128 153, 171) In some instances it appears that the occluding material comprises chiefly clumped platelets with some fibrin In the small arteries and arterioles proliferated and/or damaged endothelial cells are sometimes seen at the base of these thrombi Over all the lesion appears to be verrucous arteritis quite comparable to valvular verrucae (128) Organization of these thrombi may result in permanent marked narrowing of these small vessels

In the light of the evidence presented here and elsewhere (123 126) to show that Aschoff bodies develop from injured myofibers it might appear tempting to consider that narrowing or occlusion of the lumen of small myocardial vessels by proliferative vascular change or by thrombosis results in the occurrence of Aschoff bodies Indeed Whitman and Eastlake (202) considered this possibility But the evidence for such a view is lacking In several cases of fatal rheumatic fever Stetson (171) reported a consistent correlation between the occurrence of leukocyte-platelet thrombi in capillaries small veins and occasionally in arterioles on the one hand and the presence of Aschoff bodies on the other In my own studies however, of many sections of heart in many cases of active rheumatic heart disease, vascular thrombi, though found in some hearts have not been found, though carefully looked for, in many others but myocardial Aschoff bodies were present in large numbers Furthermore in fatal cases of thrombotic thrombocytopenic purpura, in which widespread platelet thrombosis of arterioles and capillaries occurs in tissues including the heart (7 122), Aschoff bodies have never been reported to occur in the myocardium I (126) have recently examined many sections of myocardium in a case of thrombotic thrombocytopenic purpura that are peppered with an extraordinarily large number of leukocyte-platelet and platelet thrombi both fresh and in various stages of organization in capillaries venules, arterioles and small arteries These thrombotic lesions are strikingly like those found in rheumatic fever Though carefully looked for several times no lesions resembling Aschoff bodies have been found in this case, but some minute infarcts were found

The earlier studies on the relationship of lesions of coronary arteries and their branches to myocardial damage were carried out without the knowledge we have recently gained that direct rheumatic injury to muscle cells is essential to the formation of Aschoff bodies and other myocardial lesions Thus in 1933 Karsner and Bayless (87) wrote as follows The increasing amount of muscle destruction and fibrosis must be due either to recurring acute cycles of rheumatic fever or to chronic arterial disease Many cases, if the history can be depended upon are monocyclic Extensive myocardial fibrosis in these cases can better be explained by chronic arterial disease than otherwise But we now know that both protracted and relatively short episodes of rheumatic activity may often not be evident clinically, and furthermore, the evidence presented here and elsewhere (123, 126) indicates that rheumatic activity directly damages muscle cells in the heart Nevertheless as has long been recognized (49, 94, 153, 174) appreciable narrowing of the lumina of coronary arteries or their myocardial branches whether caused by proliferated intimal elements thrombosis, or by the two combined very probably interferes with myocardial nutrition, and such vascular lesions of small vessels may well lead to micro-infarcts as Krehl (94) and Romberg (153) long ago and others (49, 87, 174) have suggested

XIII RHEUMATIC DISEASE OF CARDIAC VALVES AND CHORDAE TENDINEAE AND RELATION OF DEFORMITY OF THESE STRUCTURES TO MYOCARDIAL FUNCTION AND FAILURE

The first known illustration of mitral stenosis is found in Vieussens classic treatise on heart disease published in 1715 (188-a) In this treatise Vieussens recorded observations made from clinical study of patients with mitral stenosis and patients with aortic stenosis and insufficiency and described these valvular changes at autopsy It is known that in 1788-89 Pitcairn (141) and Jenner (84) recognized from clinical observation that the heart is not infrequently injured in attacks of rheumatic fever Bouillaud (21 22) and Watson (195a) in 1835–40 emphasized that attacks of rheumatic fever frequently result in damaged cardiac valves and pericardium Bouillaud described various stages of the valvular disease in the gross from early inflammatory changes sometimes associated with verrucae to marked thickening and hardening with deformity of valves Watson described rheumatic verrucae thickening and puckering of valves observed that the mitral and aortic valves were most commonly affected and gave a classic description of rheumatic fibrinous pericarditis

With the rise of the science of bacteriology in the last quarter of the 19th century numerous efforts were made to identify microorganisms causative of rheumatic fever Several observations were reported of bacteria in valvular lesions of rheumatic patients and growth of various bacteria was reported in cultures made at autopsy from valves of such patients In the case of many of these reports it appears that rheumatic valvulitis was confused with bacterial valvulitis (bacterial endocarditis) It further appears that at that time the importance of aseptic surgical technique in post mortem cultures of valves was very probably not appreciated

At that time differences in the interpretation of the nature of valvular verrucae developed In 1880 and again in 1896 Neumann (131 132) as mentioned previously in section IV of this monograph stated that verrucae are formed entirely from valvular connective tissue that undergoes fibrinoid metamorphosis Marchand (116) and Ziegler (204-a) on the other hand considered verrucae to represent thrombotic deposit on inflamed valve surfaces To Ziegler verrucae represented thrombo-endocarditis

Bulloch (25-a) and Coombs (39) observed that the earliest rheumatic change in the valves occurs beneath the endothelium and deep within the valvular substance and that the formation of verrucae is of later occurrence There is often intense proliferation of valvular cells including Anitschkow myocytes and fibroblasts and multinucleated cells may be found Infiltration with lymphocytes and plasma cells occurs Sometimes in a fulminating attack of rheumatic fever many polymorphonuclear leukocytes may be found Proliferation sometimes focal and at other times more extensive of valvular endothelial cells and cells beneath the endothelium sometimes occurs in palisade like arrangement These proliferated cells are often basophilic and sometimes multinucleated We (127 128) have produced in rabbits valvular lesions very closely resembling these rheumatic valvular changes by repeated focal infections with group A streptococci Acellular non bacterial verrucae appear to be secondary to proliferation and necrosis of the most superficially proliferated valvular cells and the verrucae probably represent small thrombi deposited on damaged proliferated endocardial cells It appears that fibrin sometimes occurs not only in verrucae but in subendothelial sites Fibrinous and serous' inflammation of valves has been discussed by Bohmig (20-a) The importance of serum components in the pathogenesis of valvular disease is as yet unknown

Valvular scarring consequent on protracted or repeated episodes of inflammation throughout the valve substance rather than the organization of valvular verrucae is now generally believed to chiefly account for the thickening of the valve leaflets and calcification creates further deformity However fibrin and platelets repeatedly laid down focally on roughened valve surfaces and incorporated in the valves over long periods of time in some subjects may partially account for valvular thickening

A review and detailed systematic study by Gross and Friedberg (71 b) of lesions of cardiac valves in rheumatic fever may be consulted In another publication these investigators emphasized the importance and common occurrence of inflammatory changes in valve rings (71 a) Lesions very closely resembling these have been

produced by us (127 128) in rabbits by repeated *focal infections with Group A streptococci* Scarring in these sites following protracted or repeated rheumatic attacks is most marked in mitral and aortic valve rings and is particularly damaging to the patient for the following reason The ring tissue constitutes the *hinges* that connect the valves to the body of the myocardium Interference with the normal movement of the valves from their bases follows scarring and deformity of the ring or hinge tissue Vascularization of scarred valves and *their rings commonly occurs and in these sites* numerous capillaries and larger vessels with greatly thickened walls may be found

The occurrence of muscle cells at the base of and in valves has been referred to in Sections VI and VII and illustrated in Figs 99–116 and rheumatic lesions of smooth muscle cells in valves are illustrated in Figs 101 102 and 108

As in the case of deformity of the valves and *their rings thickening shortening and fusion* of chordae tendineae result from protracted or repeated rheumatic inflammation of these structures and importantly contributes to alteration of valvular function Scarring of papillary muscles also plays a role in this alteration

That valvular deformity places an important and sometimes disabling burden on the myocardium is clear In the case of the mitral valve *marked obstruction to the flow of blood* from left atrium to left ventricle caused by marked or tight mitral stenosis is often followed by over distention of the left auricle stasis of blood in the atrium and pulmonary hypertension Stasis of blood in the left auricle may result in development of thrombus from which emboli may arise *The burden placed on atrial muscle cells leads to their hypertrophy and at least* contributes to eventual fatigue and alteration of their function Marked tricuspid stenosis results in over-distension of the right atrium and passive engorgement of the liver Aortic incompetence due to deformity of the aortic valve place an important burden on the left ventricle and considerable aortic incompetence for many years may be associated with great hypertrophy of the left ventricle The author is mainly in *agreement* with Coombs (39) that injury to the mitral cusp is not the chief *factor* in the production of mitral regurgitation in rheumatic heart disease It is to the myocardial factor that we must look for an explanation of mitral insufficiency As Coombs further wrote post rheumatic sclerosis of the valves limits cardiac efficiency when it produces *1) obstruction with or without constriction at the* auriculo ventricular openings, in which cases the immediate burden is borne by the corresponding atrium 2) Incompetence with or without obstruction at the orifice of the aortic or pulmonary artery in which cases it is the corresponding ventricle that bears the burden

The lack of correlation between the degree of mitral stenosis and cardiac disability has been *discussed in Section XI of this communication It* is also known as discussed in Section XI that some persons with marked mitral stenosis can live to advanced age with little or no signs of congestive heart failure Other patients with similar degree or less mitral stenosis on the other hand develop congestive heart failure in the 3rd decade or earlier These clinical observations taken together appear to point to the *great importance of the condition of the myocardium* in rheumatic heart disease The marked *improvement following mitral commissurotomy* of many patients with mitral stenosis may be interpreted to show that relief of the obstruction has removed an important burden that the myocardium cannot well tolerate

XIV Summary of The Author s Conception of the Origin of Various Rheumatic Lesions Including the So-Called Aschoff Bodies From Muscle Cells of The Heart and of The Relation of These Lesions to Heart Failure

Our findings in the heart of rabbits that died or were sacrificed while sick following repeated focal infections with group A streptococci and in the heart of patients who died with active rheumatic heart disease demonstrate that the characteristic constituents of myocardial Aschoff bodies are of two types 1) mono- multi or nonnucleated fragments of damaged muscle cells *(Fig 28–45 70 72 74 77 and 80) and 2)* multinucleated syncytial masses of myogenic *origin that proliferate from inside the sarcolemma* into tracks of disintegrating muscle cells and appear in the beginning to represent attempt at regeneration of heart muscle cells (Fig 10–18 52 53 57 and 59) The various rheumatic lesions of heart muscle cells may be viewed as occurring in zones of a spectrum with

reference to reaction of the cells to rheumatic injury as follows 1) In a zone at the left end of the pectrum is necrosis of muscle cells sometimes with no inflammatory reaction but often with infiltration of varying numbers of inflammatory cells among which are interspersed mono- and nonnucleated myofiber fragments (Figs 145 and 149) Such lesions are probably the result of intense rheumatic injury The wider the extent of injury the more diffuse are the lesions Extensive le ions in this zone have probably been most often found in children who have experienced a stormy clinical course with rapidly fatal outcome 2) In the next zone is focal necrosis of muscle cells with less some times little infiltration of inflammatory cells but with mono and nonnucleated myofiber fragments In addition there is proliferative nuclear change in the form of an occasional mul *tinucleated myofiber fragment and/or multi* nucleated syncytial myogenic mass that repre sents attempt at regeneration Thus in this zone are lesions like those seen in Figs 50 52 54 57 59 84–89 147 157 and 160 that are generally re ferred to as Aschoff bodies The e lesions are not as florid as those in the next zone 3) Then there is a zone of focal necrosis of muscle cells often with very little infiltration of inflammatory cells but with mono- and nonnucleated myofiber fragments and more prominent than in the previous zone is proliferative nuclear change in the form of multinucleated myofiber fragments and multinucleated syncytial myogenic masses that have proliferated inside the arcolemma in attempt at regeneration of muscle Thus in this zone occur florid Aschoff bodies (Fig 2 13 27 73 82 and 159) 4) Then there may be a zone of focal damage to mu cle cells where although less intense injury occurs the cells do not survive but regeneration of an occasional cell *may* occur 5) Finally in a zone at the right end of the spectrum there occurs impairment of mu cle cells that results from still le s severe injury and the cells survive

In the case of the lower grades of rheumatic injury to heart muscle cells subtle changes may not be observed on study by light microscopy However in some patients when such impair ment is widespread the clinician may detect as he can in the case of more severe myocardial dis ease the over all alteration of myocardial func tion as manifested by cardiac dilatation with consequent widening of the mitral valve ring which can result in apical murmurs by heart sounds that are slurred muffled or of other poor quality and by changes in the electrocardio graphic pattern But in other patients these lower grades of rheumatic di ease of heart mu cle may not be detected by the persevering clin ician on careful daily examination even with the aid of the electrocardiograph and fluoroscope

All or various combinations of the reactions of heart muscle cells to rheumatic injury occur in one case of active rheumatic heart disease and sometimes many of these reactions may be seen in one low power field (Fig 150)

It has al o been here demonstrated that in cardiac atrial appendage rheumatic subendo cardial lesions generally referred to as Aschoff bodies are of two kinds 1) Aschoff bodies that originate from rheumatic damage to (striated) *heart muscle cells* (Figs 82–86 and 88–90) just subjacent to the subendocardial zone of smooth *mu cle and connective tissue In expanding such* A choff bodies sometimes come to lie partially in the smooth muscle connective tissue zone 2) Lesions generally de ignated A choff bodies that lie entirely in the subendocardial smooth mu cle connective tissue zone and originate from rheu matic damage to *smooth muscle cells* (Figs 94 and 97) and some of these lesions can resemble to varying degrees Aschoff bodies that are de rived from heart mu cle cells Finally the oc currence in rheumatic heart disease of focal lesions of smooth muscle cells in heart valves (Figs 101 102 and 108) and in myocardial arteries (Figs 118–120 and 123–135) is also here illustrated and such lesions can occasionally re semble Aschoff bodies

The various rheumatic changes of heart mus cle cells must be considered collectively and together with valvular deformities when pres ent in explanation of altered function and failure of the heart In mo t fatal cases of ac tive rheumatic heart disease with little or no valvular deformity it appears that Aschoff bodies e pecially the florid one do not occur in great enough number to account in themselves for myocardial failure In many of the e cases especially in children the occurrence of le ions of heart mu cle cells with no or little prolifera tive nuclear change (as found in zones 1 and 2 outlined above) is a more prominent feature than the occurrence of lesions of heart muscle cells with greater proliferative nuclear change (as found in florid A choff bodies of zone 3) As compared with the intensity and extent of active

rheumatic disease of heart muscle necessary to cause failure of hearts without valvular deformities the intensity and extent of active rheumatic disease of heart muscle that can precipitate failure of hearts burdened with valvular deformities and/or damage of heart muscle caused by previous injury is probably considerably less In the latter cases where the heart is burdened by severe valvular deformity the less severe myocardial changes found in lesions in zones 4 and 5 if widespread may precipitate failure of the heart Although they may not be as important to altered function and failure of the myocardium as the other rheumatic lesions of heart muscle cells taken together Aschoff bodies in themselves are important and unequivocal evidence of *active* rheumatic heart disease Furthermore our findings here illustrated taken together with findings of others (28 41 96 102 108 118 180) make it plain that the occurrence of active specific rheumatic lesions of muscle cells found in biopsied atrial appendage at the time of surgery of rheumatic hearts signifies the great likelihood of active rheumatic disease of ventricular heart muscle cells

Epilogue

Knowledge of how the heart reacts to injury in rheumatic heart disease is important to understanding of how the heart is injured in this disease and essential to understanding of the natural history of the disease In 1898 Lees and Poynton reported their demonstration of the common occurrence of cardiac dilatation often marked and usually transient in primary and repeated attacks of rheumatic heart disease in children and young adults Poynton commented on the discrepancy between marked cardiac dilatation and slight morphologic alterations observed microscopically in the myocardium in fatal cases with or without appreciable valvular changes These myocardial alterations comprising occasional foci of fatty change in heart muscle fibers and foci of cellular exudation between the muscle fibers he deemed inadequate to account for the cardiac dilatation He was of the opinion however that not only in children but in adults as well active rheumatism injuring the heart muscle is probably of great importance to cardiac failure

In 1907 Coombs reported that the signs of heart disease in the many rheumatic children studied by him were in the great majority of cases referable to ventricular dilatation and its corollary mitral incompetence" He further stated "It is I think straining at a gnat and swallowing a camel to suppose that tiny pinhead granulations on the valves are responsible for mitral insufficiency and to ignore the very considerable stretching of the mitral ring After many years of intensive clinical and histopathologic study of rheumatic heart disease he emphasized in 1924 that active rheumatic alteration of heart muscle is the very probable cause of cardiac dilatation and failure in children with rheumatic heart disease and may be of great importance to cardiac failure in adults with this disease Yet in fatal cases the only changes that he observed in heart muscle cells were cloudy swelling in very acute cases that was never very intense and occasional foci of fatty metamorphosis in some cases With respect to this discrepancy he commented as follows

These are trifling changes but so are those found in most forms of myocardial failure This discrepancy between functional impairment and apparent anatomic integrity is due to the inadequacy of histologic methods It is to be hoped that someone will find a way of demonstrating clearly finer alterations within the cells of the cardiac muscle Coombs regarded the characteristic rheumatic submiliary nodules in the myocardium as non myogenic lesions of interstitial connective tissue

In 1933 Sir Thomas Lewis wrote concerning chronic rheumatic heart disease as follows

Congestion is the usual termination in cases of rheumatic heart disease Failure is due in part to the unusual burdens of work that the heart has to bear such as valve defects of various kinds and sometimes strong adhesions for these deplete reserves But the chief factor nevertheless must be inherent in the muscle itself for failure can occur without the increased burden And yet muscle that has failed cannot at present be recognized histologically or biochemically There is increase of the interstitial fibrous tissue a little atrophy here and there a little fatty change for the most part the fibers seem sound and the muscle presents no more change than is often found in hearts that have not failed The change in the quality of the muscle is more subtle and frequently it is brought about by some recent infection from which the patient has suffered Not only a rheumatic infection but infec

tions of other types endanger or terminate the lives of those who are near to congestion or actually display it

The above passage was written when the concept that rheumatic myocardial lesions are essentially non myogenic reactions of connective tissue was approaching culmination This passage is also found in the fourth and last edition of Lewis book *Diseases of the Heart* published in 1946 when rheumatic fever was becoming widely known as a collagen disease or disease of connective tissue Then as now the essential involvement of muscle cells in characteristic and other rheumatic lesions of the myocardium was little recognized and then as now the relation of these myocardial lesions very widely thought to be connective tissue lesions to the altered function and failure of the myocardium in rheumatic heart disease was generally poorly understood

Evidence here presented and illustrated demonstrates the origin of rheumatic myocardial lesions including the so-called Aschoff bodies from heart muscle cells themselves and the origin of certain other rheumatic cardiac lesions from smooth muscle cells If active rheumatic disease of heart muscle cells can cause failure of children s hearts without the burden of valvular deformity then it is likely that active rheumatic disease of heart muscle cells can cause failure of adult hearts especially those burdened with valvular deformity and with myocardium damaged by previous attacks Derived from experiment and histopathologic study findings here presented and viewed in relation to clinical observations provide strong evidence of the very important causative relation of rheumatic disease of heart muscle cells to altered function and failure of the heart in acute and chronic rheumatic heart disease in children and adults

Finally it appears that results in part here illustrated of repeated focal infections with group A streptococci in rabbits contribute to understanding of how rheumatic heart disease is caused These experiments are being continued

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COLOR PLATES FOLLOW

The photolithographs that follow provide evidence of the origin of Aschoff bodies and other lesions from muscle cells in rheumatic heart disease This evidence stems from the experimental induction of myocardial lesions closely resembling those of human rheumatic heart disease, in a small proportion of many rabbits of random stock that were repeatedly infected focally with group A streptococci of different serological types The results of these experiments provide evidence that Aschoff bodies and other myocardial lesions in human rheumatic heart disease develop in response to repeated focal infections with group A streptococci even though these lesions develop in only a small proportion of the many in the random population so infected Detailed microscopic study of the experimentally induced myocardial lesions resulted in the finding that these lesions are derived from injury to heart muscle cells This experimental investigation led to extensive direct evidence of the origin of Aschoff bodies and other myocardial lesions from heart muscle cells in human rheumatic heart disease These latter findings have resulted from detailed microscopic study of the heart of over 90 patients who died with active rheumatic heart disease and from study of the left atrial appendage removed from over 100 other patients at the time of mitral commissurotomy and the evidence so obtained and here illustrated is in contrast with the widely accepted theory that these are primarily and essentially lesions of collagen and/or other components of connective tissue Furthermore study of myocardial arteries and atrial appendages led to the finding of the origin of certain rheumatic lesions from smooth muscle cell [illegible] and [illegible] f these latter lesions can as here illustrated resemble Aschoff b[illegible] [illegible] derived from (striated) heart muscle cells Also illu[illegible] [illegible] f smooth muscle and striated muscle in valves [illegible] photographic evidence of the close [illegible] Aschoff bodie[illegible] in man and experimentally induced [illegible]

The photomicrographs were [illegible] Andrew H [illegible] Jr and the author on Kodachrome type F 35 mm film

The lithographic reproductions w[illegible] the Hallmark Colormaster C[illegible] process without hand ret[illegible] etching To attain color fid[illegible] and sharpness of [illegible] all color correction has been achieved phot[illegible]hanically

INTRODUCTION TO ILLUSTRATIONS

The photolithographs that follow provide evidence of the origin of Aschoff bodies and other lesions from muscle cells in rheumatic heart disease This evidence stems from the experimental induction of myocardial lesions closely resembling those of human rheumatic heart disease in a small proportion of many rabbits of random stock that were repeatedly infected focally with group A streptococci of different serological types The results of these experiments provide evidence that Aschoff bodies and other myocardial lesions in human rheumatic heart disease develop in response to repeated focal infections with group A streptococci even though these lesions develop in only a small proportion of the many in the random population so infected Detailed microscopic study of the experimentally induced myocardial lesions resulted in the finding that these lesions are derived from injury to heart muscle cells This experimental investigation led to extensive direct evidence of the origin of Aschoff bodies and other myocardial lesions from heart muscle cells in human rheumatic heart disease These latter findings have resulted from detailed microscopic study of the heart of over 90 patients who died with active rheumatic heart disease and from study of the left atrial appendage removed from over 100 other patients at the time of mitral commissurotomy and the evidence so obtained and here illustrated is in contrast with the widely accepted theory that these are primarily and essentially lesions of collagen and/or other components of connective tissue Furthermore study of myocardial arteries and atrial appendages led to the finding of the origin of certain rheumatic lesions from smooth muscle cells and some of these latter lesions can as here illustrated resemble Aschoff bodies that are derived from (striated) heart muscle cells Also illustrated is the occurrence of smooth muscle and striated muscle in valves of the heart Submitted first is photographic evidence of the close resemblance between Aschoff bodies in man and experimentally induced myocardial lesions in rabbits

The photomicrographs were taken by Andrew H Littell Jr and the author on Kodachrome type F 35 mm film

The lithographic reproductions were made in four colors by the Hallmark Colormaster Control process without hand retouching or dot etching To attain color fidelity and sharpness of detail all color correction has been achieved photomechanically

[illegible]

[illegible]

... of the heart of ... [illegible] ... and from study of ... [illegible] 100 other patients at the time ... so obtained and here illustrated [illegible] ... that the ... [illegible] ... other components of connective tissue and vessel appendages ... rheumatic lesions from smooth muscle ... here illustrated ... (striated) heart muscle cell ... muscle and striated muscle ... graphic evidence of the ... and experimentally induced ... [illegible]

[illegible] ... and the evidence ... of collagen and ... study of unrelated ... of the ... [illegible] ... these latter lesions ... are derived from ... smooth ... photo... [illegible]

The photomicrographs were taken by ... [illegible] ... and the author on Kodachrome type ... 35 mm. ...

The lithographic reproductions were made ... by the Hallmark Colormaster Control process without hand ... etching. To attain color fidelity and sharpness of detail ... correction has been achieved photomechanically.

EXPLANATION OF PLATES

Fig 1 From the left ventricle of rabbit 80 65 sacrificed while quite sick 12 days after onset of the second focal cutaneous infection with group A streptococci Although repeated blood cultures were negative this animal received large amounts of penicillin intramuscularly from the 5th to 11th day following the last infection in an attempt to enhance chance for recovery

Two focal myocardial lesions closely resembling the human Aschoff bodies in Fig ? Hematoxylin and eosin × 322

Fig 2 From the left ventricle of a 20 year old man who died during the third recognized attack of rheumatic fever (autopsy 12278 New York Hospital)

Two Aschoff bodies in myocardium Hematoxylin and eosin × 200

Fig 3 From the left ventricle of the rabbit referred to in Fig 1

Focal myocardial lesions resembling the human lesions in Fig 2 Hematoxylin and eosin × 200

Fig 4 From the left ventricle of a 7 year old girl who died during an attack of acute rheumatic fe er (autopsy 37034 Bellevue Hospital)

Aschoff body very near a small myocardial artery Note close resemblance to the rabbit lesion in Fig 5 Giemsa × 200

Fig 5 From the interventricular septum of rabbit 70 55 that died 8 days after the last of 8 focal cutaneous infections with group A streptococci

Myocardial lesion closely resembling the human Aschoff body in Fig 4 very near a myocardial artery Masson trichrome × ?00

Fig 6 From the same block of tissue of the patient referred to in Fig 2

Aschoff body in myocardium Hematoxylin and eosin × 200

Fig 7 From the left ventricle of the rabbit referred to in Figs 1 and 3

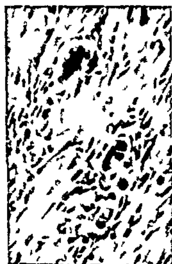
Myocardial lesion Note the marked similarity between this lesion and the human lesion in Fig 8 with respect to the multinucleated mass in the lower portion of each lesion and the myofiber fragment extending upwards from it Hematoxylin and eosin × 322

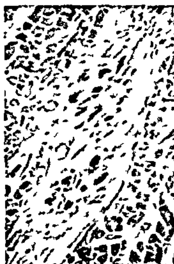
Fig 8 From the left ventricle of a 17 year old girl who died during the last of several attacks of rheumatic fever (autopsy 179 Ro kefeller Institute Hospital)

Aschoff body in myocardium Note the marked similarity between this human lesion and the rabbit lesion in Fig 7 with respect to the multinucleated mass in the lower portion of each lesion and the myofiber fragment extending upwards from it Hematoxylin and eosin × 322

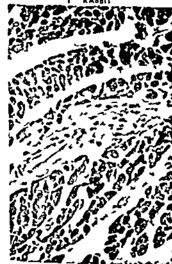
Fig 9 From the left ventricle of rabbit 85 30 that died 11 days after the last of 3 focal cutaneous infections with group A streptococci Two myocardial lesions Note the resemblance of the upper lesion to the human Aschoff body in Fig 6 also note the basophilia of m ny cells in both of the rabbit lesions (Basophilia of individual heart muscle cells evident in several figures in the last plate of photographs) Hematoxylin and eosin × 32?

CLOSE RESEMBLANCE BETWEEN ASCHOFF BODIES IN MAN AND EXPERIMENTALLY INDUCED MYOCARDIAL LESIONS IN RABBITS


1 RABBIT


2 HUMAN


3 RABBIT


4 HUMAN


5 RABBIT


6 HUMAN


7 RABBIT


8 HUMAN

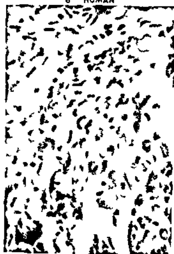

9 RABBIT

Fig 19 From the left ventricle of a 12 year old girl who died 2 years after the first recognized attack of rheumatic fever and 1 month after onset of an upper respiratory infection (autopsy 12873 New York Hospital)

Early disintegration of a small bundle of myofibers between larger bundles Hematoxylin and eosin × 200

Fig 20 From the left ventricle of the patient referred to in Figs 2 and 6

Disintegration of a bundle of myofibers between larger bundles Hematoxylin and eosin × 00

Fig 21 From the patient referred to in Figs 2 6 and 20

Two small bundles of myofibers between larger bundles Hematoxylin and eosin × 200

Fig 22 From the left ventricle of a 12 year old boy who died about 6 weeks after the beginning of the fifth recognized attack of rheumatic fever (autopsy 9609 New York Hospital)

A bundle of myofibers between larger bundles Hematoxylin and eosin × 200

Fig 23 From the left ventricle of the patient referred to in Figs 2 6 20 and 21 Alteration of a bundle of myofibers between larger bundles

This alteration further advanced than that in Figs 19 20 and 21 is recognizable as an Aschoff body and the pink staining sarcoplasmic masses might be misinterpreted as altered collagen Hematoxylin and eosin × 200

Fig 24 From the left ventricle of the patient referred to in Figs 2 6 20 21 and 23

Disintegrating bundles of myofibers between larger bundles Hematoxylin and eosin × 3??

Fig 25 From the left ventricle of a 17 year old female who died during the fourth known attack of rheumatic fever (autopsy 9600 New York Hospital)

In the lower portion of the picture is a bundle of myofibers the left portion of which is evolving into an Aschoff body This bundle is between larger bundles In the right upper portion is an Aschoff body very probably derived from a muscle bundle situated very much like the bundle in Fig 22 with respect to contiguous muscle Hematoxylin and eosin × 80

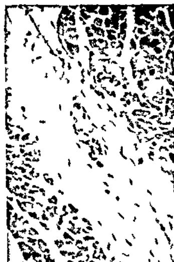
Fig 26 From the left ventricle of a 60 year old woman who died 30 years after the only recognized attack of rheumatic fever and 20 years after the beginning of many episodes of congestive heart failure (autopsy 15510 New York Hospital)

A bundle of myofibers between larger bundles Disintegration of a portion of the central bundle with a multinucleated structure Many further developed and characteristic Aschoff bodies throughout the myocardium were found Hematoxylin and eosin × 500

Fig 27 From the left ventricle of the patient referred to in Figs 2 6 20 21 23 and 24

Disintegration of a bundle of myofibers between larger bundles This disintegration that has proceeded further than that in Figs 20 21 and 24 is recognizable as an Aschoff body Hematoxylin and eosin × 322

ORIGIN OF ASCHOFF BODIES FROM HEART MUSCLE FIBERS IN SMALL BUNDLES BETWEEN LARGER ONES


19 HUMAN

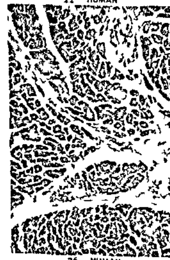

20 HUMAN

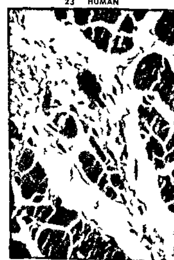

21 HUMAN


22 HUMAN


23 HUMAN


24 HUMAN


25 HUMAN


26 HUMAN


27 HUMAN

Fig 28 From the left ventricle of a 25 year old girl who died 19 years after a protracted attack of polyarthritis associated with subcutaneous nodules 5 months after development of bilateral ankle edema and 1 week to 10 days after onset of marked dyspnea associated with an upp r respiratory infection (autopsy 17823 New York Hospital)

Heart muscle fiber with three nuclear masses and a small area of interrupted myofibrils just below the upper nucleus Many Aschoff bodies were found throughout the myocardium Hematoxylin and eosin × 500

Fig 29 From the left ventricle of the heart referred to in Fig 28

The myofiber in the center shows multiple nuclei in the upper portion and multiple nuclei in the lower portion Probable fragmentation of the myofiber just below the upper group of nuclei Hematoxylin and eosin × 500

Fig 30 From the left ventricle of a 12 year old girl who died after several attacks of rheumatic fever in the previous 5 years and about 3 weeks after the onset of an upper respiratory infection (autopsy 9208 New York Hospital)

A heart muscle fiber has split into 4 fragments with multiple nuclei in each fragment This is a stage of fragmentation later than the one seen in Fig 29 Hematoxylin and eosin × 500

Fig 31 From the left ventricle of a 23 year old girl who died after 4 recognized attacks of rheumatic fever 2½ years after onset of progressive congestive heart failure and 16 months after the insertion of a plastic valve in the aorta for aortic insufficiency (autopsy 16211 New York Hospital)

Fragmentation of a myofiber is obvious and the fragments are further apart than those in Fig 30 Many Aschoff bodies were found in the heart Hematoxylin and eosin × 500

Fig 32 From the left ventricle of the patient referred to in Fig 18

Fragmentation of a myofiber strikingly similar to that in Fig 31 with the multinucleated fr g ments about the same distance apart as in Fig 31 Connective tissue normal in appearance This lesion is in the center of a large Aschoff body derived from a bundle of myofibers between larger bundles of myofibers Masson trichrome × 500

Fig 33 From the interventricular septum of a 13 year old girl who died about 6 weeks after onset of an upper respiratory infection and about 3 weeks after recognition of active rheumatic heart disease (autopsy 716 Rockefeller Institute Hospital)

Lining up of myofiber fragments some with one nucleus some with multiple nuclei and some with no nuclei strikingly like the lining up of fragments in a row seen in Fig 30 above This picture represents most of an Aschoff body deri ed from a bundle of myofibers lying between larger bundles of myofibers The connective tissue appears normal Masson trichrome × 500

Fig 34 From the left ventricle of the patient referred to in Fig 31 above Splitting of a myofiber into 3 fragments each with multiple nuclei and slightly basophilic sarcoplasm Hematoxylin and eosin × 200

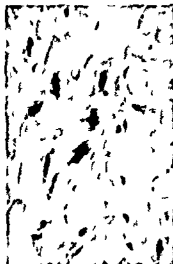
Fig 35 Higher magnification of the fragment in the lower portion of Fig 34

Note large number of nuclei in fragment Hematoxylin and eosin × 500

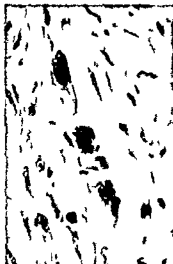
Fig 36 From the left ventricle of the patient referred to in Figs 8 and 16

Basophilic myofiber fragment containing over 30 nuclei Eosin and methylene blue × 500

SPLITTING OF HEART MUSCLE FIBERS INTO FRAGMENTS SOME MULTINUCLEATED IN RHEUMATIC HEART DISEASE


28 HUMAN

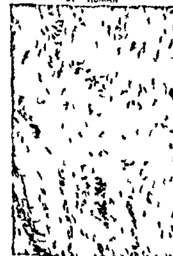

29 HUMAN


30 HUMAN


31 HUMAN


32 HUMAN


33 HUMAN


34 HUMAN


35 HUMAN


HUMAN

Fig 37 From the interventricular septum of the patient referred to in Fig 33
Myofiber very close to a small myocardial blood vessel Hematoxylin and eosin × 372

Fig 38 From the left ventricle of the patient referred to in Fig 26
Myofiber with 2 nuclei very close to a small myocardial blood vessel Masson trichrome × 640

Fig 39 From the left entricle of the heart referred to in Fig 30
Multinucleated myofiber very close to a small myocardial blood vessel Hematoxylin and eosin × 798

Fig 40 From the left ventricle of the patient referred to in Figs 8 16 and 36
Basophilic multinucleated myofiber very near a myocardial blood vessel Eosin and methylene blue × 500

Fig 41 From the left ventricle of the patient referred to in Figs 8 16 36 and 40
Two basophilic and multinucleated portions of a myofiber slung like a hammock around a small myocardial blood vessel By focusing with the microscope one can just see connection between these two fragments Eosin and methylene blue × 1250

Fig 42 From the left ventricle of the patient referred to in Fig 4
Slightly basophilic multinucleated myofiber fragment close to a myocardial blood vessel Hematoxylin and eosin × 680

Fig 43 From the left ventricle of the heart referred to in Fig 15
Fresh splitting of a myofiber into 2 multinucleated basophilic fragments ry near a capillary between large bundles of myofibers Hematoxylin and eosin × 500

Fig 44 From the left entricle of a 10 year old boy who died after 3 mo ths of recognized active rheumatic heart disease (autopsy 325 Rockefeller Institute Hospital)
Myofiber in intimate relationship to a small myocardial blood vessel Weigert hematoxylin × 500

Fig 45 From the left ventricle of the patient referred to in Figs 26 and 38
Myocardial lesion in intimate association with a myocardial blood vessel and very probably representing fragmentation of a myofiber such as that very close to a blood vessel in Fig 44 Masson trichrome × 500

MULTINUCLEATED HEART ...
VERY CLOSE TO BLOOD V...

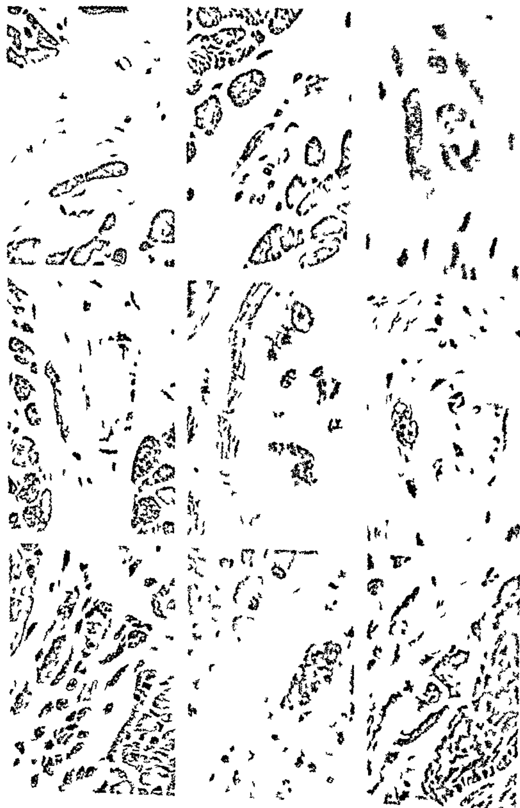


Fig 55 From the left ventricle of the heart referred to in Figs 2 6 20 21 23 24 27 50 and 54

Aschoff body derived from a bundle of myofibers between larger bundles Note the ghost like remnants of myofibers that represent myofiber disintegration further advanced than that seen in the same patient in Figs 20 21 and 24 Note also the slightly basophilic portion of a myofiber *shaft near the right lower portion of this figure* and like that in the rabbit myocardial lesion in Fig 7 and that in the human lesion in Fig 8 and note the annular arrangement of nuclei at the top central portion that closely resembles the rabbit skeletal muscle lesion in Fig 56 and the human myocardial lesions in Figs 5(and 61 (same patient) and Fig 59

This illustrates as do Figs 19 27 how so-called interstitial Aschoff bodies arise from bundles of myofibers between large bundles Hematoxylin and eosin × 322

Fig 56 From skeletal muscle of rabbit 82 45 that was sacrificed after marked weight loss and while quite sick 9 weeks after the last of 3 focal infections with group A streptococci

Interstitial valvulitis tiny (microscopic) verrucae on mitral valve acute proliferati e change *in chordae tendineae* and fresh focal myocardial lesions were evident *Skeletal muscle lesion* occurring entirely within the sarcolemma of a myofiber and showing annular arrangement of myogenic nuclei around disintegrated sarcoplasm Note close resemblance to the other annular lesions *in figures in this plate No connective tissue reaction present* Hematoxylin and eosin × 500

Fig 57 From the same patient referred to in Figs 2 6 20 21 23 24 27 50 54 and 55

A tiny Aschoff body strikingly like the rabbit skeletal muscle lesions in Figs 56 and 58 and the human myocardial lesions in Figs 59 and 61 Note the annular arrangement of nu lei around disintegrated sarcoplasm Such a sarcoplasmic mass is often incorrectly considered to b swollen collagen Hematoxylin and eosin × 500

Fig 58 From skeletal muscle of rabbit 86 38 that died many months after the third focal infection with group A streptococci

Changes within skeletal muscle cells like that in Fig 56 with myogenic nuclei nong and around sarcoplasmic material Hematoxylin and eosin × 322

Fig 59 From the left ventricle of the patient referred to in Figs 4 42 and 52

Focal myocardial lesion with annular arrangement of myogenic nuclei around a sa oplasmic mass like that in Figs 56 57 58 and 61 The sarcoplasmic core of this little lesion might be mistaken for altered collagen The figure here illustrated is a further cut of the lesion llustrated *in Fig 52 and Fig 52 illustrates even more clearly the sarcoplasmic fragment with the mult nucleated* syncytial structure surrounding it Hematoxylin and eosin × 798

Fig 60 From the left ventricle of the patient referred to in Figs 2 6 20 21 23 2(?7 50 54 55 and 57

Tiny focal myocardial lesion showing disintegration of sarcoplasm like that in Figs 50 and 54 (same patient) This little lesion derived from muscle would be referred to by some as small cell coronal Aschoff body and *the sarcoplasmic core of such a lesion is incorrectly inter) reted* by many as a swollen mass of collagen Hematoxylin and eosin × 500

Fig 61 From the left ventricle of the patient referred to in Figs 2 6 20 21 23 24 ?7 50 54 55 57 and 60

Annular arrangement of nuclei at the periphery of a sarcoplasmic mass like that in Figs 55 59 Hematoxylin and eosin × 500

Fig 62 From skeletal muscle of the rabbit referred to in Fig 58

Annular arrangement of myogenic nuclei within a sarcoplasmic mass Note the striking resemblance to the human myocardial lesion in Fig 63 *Hematoxylin and eosin* × 500

Fig 63 From the left ventricle of the patient referred to in Figs 2 6 20 21 23 24 7 50 54 55 57 60 and 61

Annular arrangement of myogenic nuclei within a sarcoplasmic mass in the myocardium Note the striking resemblance to the rabbit skeletal muscle lesion in Fig 62 Hematoxylin and osin × 500

ANNULAR PROLIFERATION OF MYOGENIC NUCLEI AROUND AND IN SARCOPLASM IN RHEUMATIC MYOCARDIAL LESIONS AND SKELETAL MUSCLE



55 HUMAN



56 RABBIT



57 HUMAN



58 RABBIT



59 HUMAN



60 HUMAN

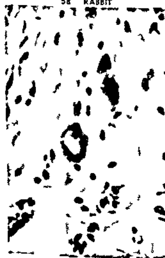






Fig 64 From the skeletal muscle of a 20 year old girl who died after several attacks of rheumatic fever 5 years after onset of progressive congestive heart failure and 11 days after mitral commissurotomy (*autopsy 16320 New York Hospital*)

Aschoff bodies were found in the myocardium The skeletal muscle lesion shown here comprises basophilic fragments of sarcoplasm and myogenic nuclei Giemsa × 500

Fig 65 From skeletal muscle of the rabbit referred to in Fig 56

Skeletal muscle lesion showing disintegration of sarcoplasm and very numerous myogenic nuclei within a sarcoplasmic mass Note normal appearance of connective tissue and the striking resemblance *of this lesion to the human myocardial lesion in Fig 68 Hematoxylin and eosin* × 500

Fig 66 From the left ventricle of the rabbit referred to in Figs 1 3 7 10 11 12 17 and 53

Multinucleated basophilic myogenic mass strikingly resembling the human myocardial one in *Fig 69 Hematoxylin and eosin* × 500

Fig 67 From skeletal muscle of the rabbit referred to in Figs 58 and 62

Multinucleated sarcoplasmic masses Note normal appearance of the connecti e tissue Hema*toxylin and eosin* × 500

Fig 68 From the left ventricle of the patient referred to in Figs 26 and 38

Multinucleated basophilic myocardial mass strikingly like the rabbit skeletal muscle lesion in Fig 65 *Hematoxylin and eosin* × 798

Fig 69 From the left ventricle of the patient referred to in Figs 31 34 and 35

Multinucleated basophilic myogenic mass strikingly like the rabbit one in Fig 66 *Hematoxylin and eosin* × 500

Fig 70 From the left ventricle of the patient referred to in Figs 44 and 48

Myofiber fragment the upper one with many nuclei Note resemblance to th *multinucleated* fragments in Figs 38 39 40 and 43 and note the relationship to contiguous my f bers str kingly like that of the myofiber in the central lower portion in Fig 71 to contiguous myof bers Weigert *hematoxylin* × 500

Fig 71 From the left ventricle of the patient referred to in Figs 44 48 and 0

Myofibers lying between large bundles of myofibers Note relationship of the n yofiber in *the central lower portion to contiguous myofibers l ke that in Fig 70 Phosphotungstic* acid hematoxylin × 322

Fig 72 From the left ventricle of the patient referred to in Figs *8 16 36* 40 and 41

A disintegrating myofiber with multi ple nuclei in the upper portion lying between large bundles of myofibers Note the empty portion of the myofiber track like that in the lower central portion in Fig 71 also note alteration of myofibers above the central one *Eosin and methylene* bl e × 500

MULTINUCLEATED STRUCTURES DEFINED IN RHEUMATIC MYOCARDIAL LESIONS AND ...IES


64 HUMAN


65 RABBIT




67 RABBIT


68 HUMAN




70 HUMAN


71 HUMAN

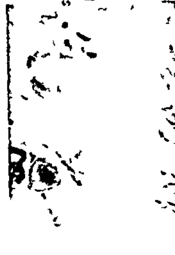


Fig 73 *From the left ventricle of the patient referred to in Figs* 26 38 45 and 68

Aschoff body in *myocardium* *The identical* section restained with Weigert van Gieson technique in Fig 76 below and *then restained with* Masson trichrome *in Fig* 79 below shows the normal appearance of the connective tissue in this Aschoff body *Hematoxylin* and *eosin* × 322

Fig 74 *From* the left *ventricle of an 8 year* old girl who died about 5½ weeks after recognition of onset of the first *recognized* attack *of rheumatic* fever (autopsy *8627 New* York Hospital)

Aschoff body *derived from myofibers lying* between large bundles of myofibers Note the normal appearance of the connective tissue and the *lining up of nucleated and non* nucleated *myofiber* fragments in a row like that in Figs 29 34 77 and 80 This lesion and those in *Figs 77 and 80* illustrate the point brought out in Figs 19 27 that interstitial Aschoff bodies are derived *from* heart muscle cells *lying* among *or* between large bundles of myofibers Masson trichrome × 400

Fig 75 From the left ventricle of a 17 month old boy who died about 7 days after complaining of pain *in* the right ankle (autopsy 6852 Mount Sinai Hospital New York)

Many Aschoff bodies were found throughout the myocardium Aschoff body very near a myocardial artery *The identical section stained* with Weigert van Gieson *in Fig* 78 immediately below shows the normal *appearance of the connective tissue in this lesion* *Hematoxylin and eosin* × 3 ?

Fig 76 Weigert van Gieson stain of *the identical* section shown in *Fig* 73 and illustrating *the normal* appearance *of the connective* tissue *within* the Aschoff body × 322

Fig 77 From the left ventricle of the patient referred to in Figs 44 48 70 and 71

Aschoff body derived from heart muscle cells among bundles of myofibers Note normal appearance of connective tissue in the lesion and the lining up of nucleated and non nucleated myofiber *fragments in a row like* that in Figs 29 34 *This illustrates the* point *brought out in Figs* 19 27 and 74 that interstitial Aschoff bodies *are derived from* heart *muscle cells lying* among *or* between bundles of myofibers Masson trichrome × 500

Fig 78 Weigert *van* Gieson *stain of* the *identical* section *shown* in *Fig* 75 and illustrating the normal appearance of the connective tissue within the Aschoff body that is very *close to a* myocardial artery (Closeness of heart muscle fibers to vessels is illustrated in Figs 37-45) × 32?

Fig 79 Masson *trichrome* stain of the *identical* section shown in Figs 73 and 76 and illustrating the normal appearance of the connective tissue within the Aschoff body × 3?2

Fig 80 Aschoff body derived from a bundle of heart *muscle* cells lying between large bundles Fragmentation of the myofibers and lining up in a row of nucleated and non nucleated *fragments* like that seen in Figs 74 and 77 and in *Figs* 29 34 Note the *delicate and normal* appearance of *the connective tissue in the Aschoff body* *Weigert* van Gieson × 250

Fig 81 Hematoxylin and eosin stain of the *identical section* of the *Aschoff* body shown in Fig 80 × 322

NORMAL APPEARANCE OF CONNECTIVE TISSUE IN ASCHOFF BODIES AND ORIGIN OF THE LESIONS FROM HEART MUSCLE CELLS



73 HUMAN



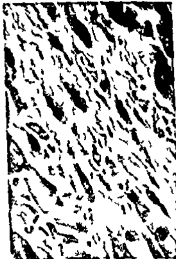
74 HUMAN



75 HUMAN



76 HUMAN



77 HUMAN



78 HUMAN





HUMAN



Fig 73 From the left ventricle of the patient referred to in Figs 26 38 45 and 68

Aschoff body in myocardium The *identical* section restained with Weigert van Gieson technique in Fig 76 below and then restained with Masson trichrome in Fig 79 below shows the normal appearance of the connective tissue in this Aschoff body Hematoxylin and eosin × 322

Fig 74 From the left ventricle of an 8 year old girl who died about 5½ weeks after recognition of onset of the first recognized attack of rheumatic fever (autopsy 8627 New York Hospital)

Aschoff body derived from myofibers lying between large bundles of myofibers Note the normal appearance of the connective tissue and the lining up of nucleated and non nucleated myofiber fragments in a row like that in Figs 29 34 77 and 80 This lesion and those in Figs 77 and 80 illustrate the point brought out in Figs 19 27 that interstitial Aschoff bodies are derived from heart muscle cells lying among or between large bundles of myofibers Masson trichrome × 400

Fig 75 From the left ventricle of a 17 month old boy who died about 27 days after complaining of pain in the right ankle (autopsy 6852 Mount Sinai Hospital New York)

Many Aschoff bodies were found throughout the myocardium Aschoff body very near a myocardial artery The *identical* section stained with Weigert van Gieson in Fig 78 immediately below shows the normal appearance of the connective tissue in this lesion Hematoxylin and eosin × 322

Fig 76 Weigert van Gieson stain of the *identical* section shown in Fig 73 and illustrating the normal appearance of the connective tissue within the Aschoff body × 322

Fig 77 From the left ventricle of the patient referred to in Figs 44 48 70 and 71

Aschoff body derived from heart muscle cells among bundles of myofibers Note normal appearance of connective tissue in the lesion and the lining up of nucleated and non nucleated myofiber fragments in a row like that in Figs 29 34 This illustrates the point brought out in Figs 19 27 and 74 that interstitial Aschoff bodies are derived from heart muscle cells lying among or between bundles of myofibers Masson trichrome × 500

Fig 78 Weigert van Gieson stain of the *identical* section shown in Fig 75 and illustrating the normal appearance of the connective tissue within the Aschoff body that is very close to a myocardial artery (Closeness of heart muscle fibers to vessels is illustrated in Figs 37 45) × 322

Fig 79 Masson trichrome stain of the *identical* section shown in Figs 73 and 76 and illustrating the normal appearance of the connective tissue within the Aschoff body × 322

Fig 80 Aschoff body derived from a bundle of heart muscle cells lying between large bundles Fragmentation of the myofibers and lining up in a row of nucleated and non nucleated fragments like that seen in Figs 74 and 77 and in Figs 29 34 Note the delicate and normal appearance of the connective tissue in the Aschoff body Weigert van Gieson × 250

Fig 81 Hematoxylin and eosin stain of the *identical* section of the Aschoff body shown in Fig 80 × 322

ORIGIN OF ASCHOFF BODIES FROM HEART MUSCLE CELLS
IN ATRIAL APPENDAGES AND LEFT VENTRICLE OF THE HEART


82 HUMAN


83 HUMAN

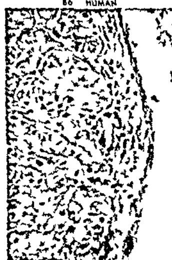

84 HUMAN


85 HUMAN


86 HUMAN


87 HUMAN





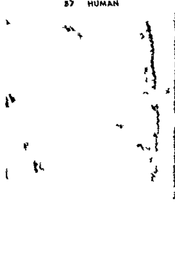


Fig 82 From the left atrial appendage removed at the time of mit a 55 year old woman with no history of rheumatic fever or chorea who nocturnal dyspnea and dyspnea on exertion 5 6 weeks prior to operation mitral stenosis with slight regurgitation was found

Aschoff bodies shown in the lower and upper central portion of the pict heart muscle cells just subjacent to the sub endocardium This point is brou pictures in this plate (S 56 7754) Hematoxylin and eosin × 80

Fig 83 From the left atrial appendage removed at the time of mitral cc 50 year old man who had polyarthritis 38 years previously and noted gradual years before operation *that progressed gradually in the last 2 years At operation* regurgitation was found

Early stage of an Aschoff body clearly representing focal disintegration of just subjacent to the sub-endocardium a little bite out of the myocardium this little wound would be expected to occur (S 57 *1479*) Masson trichrome ×

Fig 84 From the left atrial appendage removed at the time of mitral co a 50 year old woman with no history of acute rheumatic fever *or* chorea Rheu diagnosed and dyspnea on exertion developed 17 years prior to operation 4 y orthopnea and ankle edema developed and about 1 year prior to operation there of symptoms At operation marked mitral stenosis with little regurgitation was fo

Aschoff body very probably in a little later stage than that in *Fig* 83 der muscle cells just subjacent to the sub endocardium Connective tissue in lesion (S 56 8148) *Masson* trichrome × 200

Fig 85 From the left atrial appendage removed at the time of operation on a 29 year old woman who had *rheumatic fe er* 17 years previously followed by pers on exertion Four years prior to operation ascites and marked ankle edema devel cardiac symptoms approximately stationary in the past 2 years At operation marked ficiency was found and no commissurotomy was carried out

An Aschoff body derived from a little bundle of heart muscle cells has thrust its toward the subendocardium Connective tissue in *lesion* appears normal (S 55 2976) and eosin × 200

Fig 86 Phosphotungstic acid hematoxylin stain of the *identical* section shown in illustrate the origin of the Aschoff body from a little bundle of heart muscle cells Conne in *lesion* appears normal (S 55 2976) × 200

Fig 87 From a 10 year *old girl* who died 10 years after an attack of chorea a rheumatic heart disease 2 years after another attack of active heart disease and 4 mo polyarthritis and steady worsening *of cardiac* status (autopsy 9531 New York Hospital)

Aschoff body derived from heart muscle cells and possibly representing a *little later* st that seen in *Fig* 84 Hematoxylin and eosin × 200

Fig 88 From the left atrial appendage *removed* at the time of mitral commissurotor 39 year old woman who had chorea 31 years previously 3½ years prior to operation acti matic heart disease was diagnosed and increased shortness of breath de eloped In the ye r operation increasing dyspnea on exertion and *orthopnea* occurred At operation marked stenosis with some regurgitation was found

Aschoff body developing from a little bundle of heart muscle cells (*S 56* 2678) Hemat and eosin × 200

Fig 89 Masson trichrome stain of the *identical* section shown in Fig 88 and illustr normal appearance of connective tissue within the lesion (S 56 2678) × 200

Fig 90 From the *left* atrial appendage of the patient referred to in Fig 82

This picture would appear to represent the following the myocardium has been eroded or back by rheumatic damage and in the process focal *Aschoff* bodies have formed collagenization the myocardial *wounds* has occurred (S 56 7754) Masson trichrome × 80

ORIGIN OF RHEUMATIC LESIONS FROM SMOOTH MUSCLE CELLS IN CARDIAC LEFT ATRIUM SMOOTH MUSCLE IN MITRAL VALVE


91 HUMAN


92 RABBIT


93 HUMAN


94 HUMAN


95 RABBIT


96 HUMAN


97 HUMAN


98 HUMAN


99 HUMAN

Fig 91 From the left atrial appendage removed at the time of mitral commissurotomy of a 34 year old woman who had chorea 22 years previously and developed dyspnea on exertion that had been severe in the past several years Marked mitral stenosis with no evident regurgitation was found

No Aschoff bodies were found in the atrial appendage This section is shown to illustrate the avenue or band of smooth muscle cells that normally occurs in the sub-endocardium of the atrial wall (S 55 4662) Phosphotungstic acid hematoxylin × 80

Fig 92 From the left atrium of rabbit 94 96 to illustrate the broad avenue or band of smooth muscle cells that occurs in the sub endocardium of the rabbit atrium as in the human Masson trichrome × 200

Fig 93 From the left atrial appendage removed at the time of mitral commissurotomy of a 34 year old woman who had rheumatic fever 27 years previously In the year prior to operation marked progression of dyspnea and orthopnea occurred At operation marked mitral stenosis without regurgitation was found

This picture shows a broad avenue or band of smooth muscle cells in the sub endocardium (S 55 270) Masson trichrome × 80

Fig 94 From the left atrial appendage removed at the time of mitral commissurotomy of a 38 year old woman who had acute rheumatic fever 32 years before operation Dyspnea developed 5 years prior to operation and was stationary until the past several months prior to operation when it became progressively severe and was attended by the development of paroxysmal nocturnal dyspnea At operation marked mitral stenosis without regurgitation was found

As the eye of the viewer moves down the avenue of smooth muscle in the sub endocardium it comes to a lesion lying in the lower portion of the avenue that is a specific rheumatic lesion resembling the Aschoff bodies that develop from heart muscle cells See higher magnification in Fig 97 (S 56 8219) Phosphotungstic acid hematoxylin × 80

Fig 95 From the left atrium of rabbit 82 42 that died several months after the last of 5 focal cutaneous infections with group A streptococci

Two focal lesions in the sub endocardium strikingly like those in the human atrial sub-endocardium in Fig 96 These lesions occur where smooth muscle is known to occur Giemsa × 200

Fig 96 From the left atrium of the patient referred to in Figs 31 34 35 and 69

Two focal rheumatic lesions in the sub-endocardium strikingly like those in the rabbit atrial sub endocardium in Fig 95 and occurring where smooth muscle is known to occur Giemsa × 80

Fig 97 Higher magnification of Fig 94 Lesion of Aschoff body type occurring in the middle of the avenue of sub endocardial smooth muscle and very probably derived from smooth muscle cells Phosphotungstic acid hematoxylin × 200

Fig 98 From the atrial appendage shown in Fig 93 to illustrate the avenue of smooth muscle in the atrial sub endocardium Masson trichrome × 80

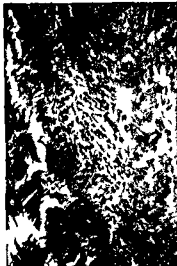
Fig 99 From the base of the mitral valve of a 12 year old girl who died 7 years after an attack of polyarthritis 2 years after another attack of rheumatic fever with congestive heart failure and 3 months after an upper respiratory infection followed by congestive heart failure (autopsy 8072 New York Hospital)

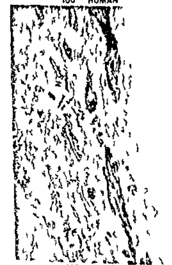
This picture illustrates the manner in which smooth muscle continues into the mitral valve from the left atrium Phosphotungstic acid hematoxylin × 32

SMOOTH MUSCLE CELLS IN HEART VALVES


100 HUMAN


101 HUMAN


102 HUMAN


103 HUMAN


104 HUMAN


105 HUMAN


106 HUMAN


107 HUMAN

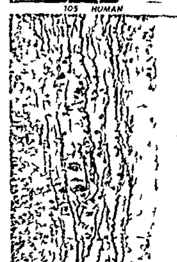

108 HUMAN

Fig 100 From the aortic leaflet of the mitral valve of a 50 year old man who died about 2 weeks after onset of an attack of activ rheumatic fever (autopsy 40 Rockefeller Institute Hospital)

Many Aschoff bodies were found throughout the myocardium This section of mitral valve shows bundles of smooth muscle that stain purple Phosphotungstic acid hematoxylin × 80

Fig 101 From the same valve referred to in Fig 100 Spindle shap d l sion resembling an Aschoff body is seen in the lower portion of the track of smooth mus le Phosphotungstic acid hematoxylin × 80

Fig 102 Higher magnification of the lesion in the lower portion of Fig 101 Phosphotungstic acid hematoxylin × 200

Fig 103 From the aortic leaflet of the mitral valve of a 24 year ol l girl who died after several attacks of rheumatic fever and with sub acute bacterial endocarditis u t became apparent several months after tooth extractions (autopsy 10488 New York Hospital)

This picture illustrates the occurrence of bundles of smooth muscle stai ng red in the mitral valve Heidenhain connective tissue stain × 80

Fig 104 From the aortic leaflet of the mitral valve of a 17 year old boy who died 9 years after an attack of chorea 4 years after a bout of active rheumatic heart disease with decompen ation and after 2 other attacks in the last 2 years of life as ociated with increas g signs of congestive heart failure (autopsy 9622 New York Hospital)

This picture shows that a considerable amount of smooth muscle stai dark purple o curs in bundles in this portion of the valve Phosphotungstic acid hematoxylin 32

Fig 105 From the aortic valve of a 28 year old man who died 18 ye after onset of chorea that recurred in the next 2 years and 2 years and 8 months respectiv ly af recurrent attacks of rheumatic fever (autopsy 9128 New York Hospital)

Note the bundles of smooth muscle staining dark purple to black beneath the valv lar endocardium Phosphotungsti acid hematoxylin × 80

Fig 106 From the aortic valve of an 11 year old girl who died af r the last of several attacks of rheumatic fever (autopsy 426 Rockefeller Institute Hospital)

This picture illustrates the occurrence of smooth muscle staining purple occurring in bun lles beneath the endocardium Phosphotungstic acid hematoxylin × 32

Fig 107 Higher magnification of Fig 106 to illustrate th occurrence f bundles of smooth muscle staining purple beneath the valvular endocardium Phosphotungstic acid hematoxylin × 80

Fig 108 From the aortic valve of the patient referred to in Figs 44 48 70 71 and 7

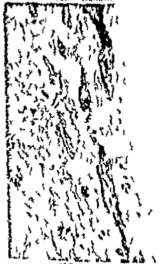
This elastic tissue stain illustrates the occurrence of smooth muscl c lls between lamina of elastic fibers basophilia and multinucleation of some of the invol ed smooth muscle cells is e id nt Weigert van Gieson × 200

SMOOTH MUSCLE CELLS IN HEART VALVES


100 HUMAN


101 HUMAN


102 HUMAN


103 HUMAN


104 HUMAN


105 HUMAN


106 HUMAN


107 HUMAN

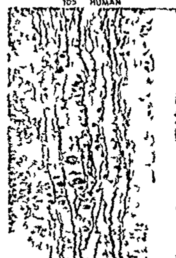

108 MAN

Fig 127 From the left ventricle of the patient referred to in Fig 25
Myocardial artery showing a focal nodular lesion in the media in the lower right portion of the picture Phosphotungstic acid hematoxylin × 80

Fig 128 Higher magnification of the nodular lesion shown in Fig 127 Phosphotungstic acid hematoxylin × 200

Fig 129 Higher magnification of the lesion shown in Figs 127 and 128
This medial lesion somewhat resembling an Aschoff body contains several multinucleated elements Phosphotungstic acid hematoxylin × 500

Fig 130 From the left ventricle of the patient referred to in Figs 76 79 80 and 81
Myocardial artery A small portion of media in the lower portion of the picture is the site of a nodule of medial cellular elements Hematoxylin and eosin × 200

Fig 131 From the left ventricle of the patient referred to in Figs 28 and 29
The media of the lower portion of this small myocardial artery is replaced by a focal lesion that contains basophilic and multinucleated cellular elements This lesion resembles an Aschoff body and is very probably derived from smooth muscle cells in the media Giemsa × 500

Fig 132 From the left ventricle of the patient referred to in Figs 87 and 115
Nodule of medial cellular elements in the right lower central portion of the media of a myocardial artery Hematoxylin and eosin × 200

Fig 133 From the left ventricle of the patient referred to in Figs 30 and 39
Nodule in the right lower portion of the media of a myocardial artery Broad zone of scarred adventitia Hematoxylin and eosin × 80

Fig 134 Higher magnification of the medial lesion shown in Fig 133 Hematoxylin and eosin × 200

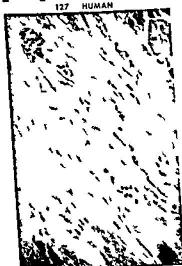
Fig 135 Higher magnification of the lesion shown in Figs 133 and 134
This lesion resembles an Aschoff body Hematoxylin and eosin × 500

ORIGIN OF RHEUMATIC LESIONS FROM SMOOTH MUSCLE CELLS IN THE MEDIA OF MYOCARDIAL ARTERIES – II

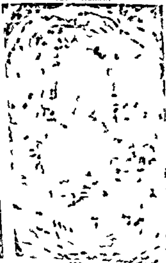

127 HUMAN


128 HUMAN


129 HUMAN


130 HUMAN


131 HUMAN


132 HUMAN


133 HUMAN


134 HUMAN


135 HUMAN

Fig 154 From the left ventricle of rabbit 81 97 that died 8 days after the last of 4 focal cutaneous infections with group A streptococci

Basophilia of heart muscle cells is here illustrated Giemsa × 500

Fig 155 From the left ventricle of the patient referred to in Figs 44 48 71 and 108

Basophilia in the upper portion of a myofiber To the right of this myofiber is cellular proliferation in tracks of necrotic myofibers like that in Figs 10 13 156 157 158 159 and in many other figures among these illustrations Hematoxylin and eosin × 500

Fig 156 From the left ventricle of the patient referred to in Figs 8 16 36 40 41 and 72

Basophilia and proliferation of nuclei in a myofiber fragment among bundles of myofibers Eosin and methylene blue × 500

Fig 157 From the left ventricle of the patient referred to in Figs 8 115 and 132

Early Aschoff body that is clearly developing from interruption and da age of heart muscle fibers that show some reactive change Note the resemblance of this lesion to the one in the atrial appendage in Fig 160 below Hematoxylin and eosin × 200

Fig 158 From the left ventricle of the patient referred to in Figs 8 16 36 40 41 72 and 156

Fragmentation and multinucleation of heart muscle cells like that in F 156 157 and 160 among many others Eosin and methylene blue × 500

Fig 159 From the patient referred to in Figs 87 115 132 and 15

An Aschoff body that has developed from heart muscle fibers shows th same multinucleated elements as seen in Figs 156 157 158 10 13 and many others Hematoxylin and eosin × 250

Fig 160 From the left atrial appendage of the patient referred to in F g 84

An Aschoff body derived from heart muscle cells near the tip of the n ocardium Note the striking resemblance to the Aschoff body above in Fig 157 Hematoxylin an l osin × 200

Fig 161 From the left ventricle of the patient referred to in Figs 8 16 36 40 41 72 156 and 158

Basophilic multinucleated myofiber mass Note the striations extending from the right portion of this mass Eosin and methylene blue × 500

Fig 162 From the left ventricle of the patient referred to in Figs 4 42 59 and 123

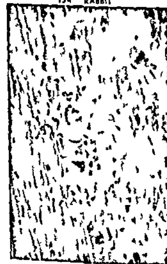
An Aschoff body with a multinucleated myogenic mass l ke that in Fig 161 nd with other nucleated and non nucleated sarcoplasmic fragments Hematoxylin and eosin × 3

ORIGIN OF THE CHARACTERISTIC RHEUMATIC MYOCARDIAL LESION FROM HEART MUSCLE CELLS

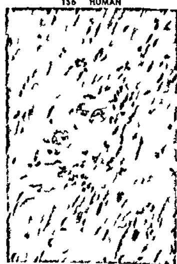

154 RABBIT


155 HUMAN


156 HUMAN


157 HUMAN


158 HUMAN


159 HUMAN


160 HUMAN


161 HUMAN


162 HUMAN

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